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A Pharmacology-Based Enrichment Program for Undergraduates Promotes Interest in Science

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There is a strong need to increase the number of undergraduate students who pursue careers in science to provide the "fuel" that will power a science and technology–driven U.S. economy. Prior research suggests that both evidence-based teaching methods and early undergraduate research experiences may help to increase retention rates in the sciences. In this study, we examined the effect of a program that included 1) a Summer enrichment 2-wk minicourse and 2) an authentic Fall research course, both of which were designed specifically to support students' science motivation. Undergraduates who participated in the pharmacology-based enrichment program significantly improved their knowledge of basic biology and chemistry concepts; reported high levels of science motivation; and were likely to major in a biological, chemical, or biomedical field. Additionally, program participants who decided to major in biology or chemistry were significantly more likely to choose a pharmacology concentration than those majoring in biology or chemistry who did not participate in the enrichment program. Thus, by supporting students' science motivation, we can increase the number of students who are interested in science and science careers.

INTRODUCTION

Many students enter college with an interest in studying science and may even contemplate careers in biomedical and behavioral sciences. However, after enrolling in introductory-level science courses, students often decide to pursue non science majors. Fewer than 40% of students who enter college with an interest in science actually complete a degree in science, technology, engineering, or mathematics (STEM) fields (President's Council of Advisors on Science and Technology [PCAST], 2012; Chen, 2013). This issue has led to the term the "leaky pipeline." Research that addresses the leaky pipeline indicates that enriched curricular opportunities and early undergraduate research experiences are important factors in enhancing students' interest in science and students' confidence in their abilities to pursue a science career (Frantz *et al.*, 2006; McGee and Keller, 2007; Russell *et al.*, 2007; Harrison *et al.*, 2011; Graham *et al.*, 2013). Moreover, there have been a number of calls to use evidence-based teaching methods to improve retention in STEM fields (Handelsman *et al.*, 2004) and to improve the quality of teaching at the college level (PCAST, 2012).

With these goals in mind, we created an undergraduate pharmacology enrichment program, building from research on best practices from educational and psychological theories of learning and motivation. We chose a pharmacology

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focus for the program, as pharmacology integrates biology and chemistry—two gateway subjects in biomedical science for undergraduates. Moreover, topics in pharmacology (e.g., how drugs work to cause or cure diseases) are especially useful for making real-world connections, one of our five motivational design principles detailed below. As we describe in the following sections, the program consisted of 1) a Summer enrichment 2-wk minicourse in pharmacology for rising sophomores at a private university in the southeastern United States and 2) a research course during the subsequent Fall semester in which students generated their own proposals and carried out empirical research.

The pharmacology enrichment program was developed based on current theories regarding students' learning and motivation. From a learning theory perspective, we sought to actively engage students in the learning process by following principles of constructivism, which emphasizes students' own construction of knowledge through active engagement with learning material (Palincsar, 1998; Hmelo-Silver *et al.*, 2007). An emphasis on active learning is certainly not new (e.g., see Ebert-May *et al.*, 1997; Dickman *et al.*, 2002), but it is often absent from undergraduate education in STEM fields. Moreover, the benefits of employing active learning are supported by current research. Active learning has been linked to higher-level learning, including problem solving and a deeper understanding of course material (Haak *et al.*, 2011; Jensen and Lawson, 2011), both of which are important for success in the sciences. A recent meta-analysis of 225 studies comparing active learning with traditional lecturing in undergraduate STEM courses indicated that the use of at least some active-learning instructional techniques was associated with an increase in student performance (assessment scores) and a decrease in failure rates (Freeman *et al.*, 2014).

Equally important is the consideration of students' motivation. Indeed, motivation becomes critically important when students face challenging course work that requires high levels of engagement, a common occurrence in STEM fields. Drawing from current motivational research on instructional supports for students' perceived competence, interest, and value for a particular subject area or field of study (Turner *et al.*, 2011; Linnenbrink-Garcia *et al.*, 2013), we identified five key motivational design principles to incorporate into our enrichment program: 1) inclusion of real-world challenging tasks, 2) provision of choice surrounding academic tasks, 3) encouragement of active involvement, 4) support for feelings of belonging, and 5) use of effort-based evaluation.

Our evaluation of the pharmacology enrichment program focused on three primary research questions. The first research question asked whether participation in an abbreviated, introductory Summer minicourse in pharmacology enhanced students' knowledge of biology and chemistry principles. Second, we examined students' overall motivation at the end of the introductory Summer minicourse and during the Spring semester after the Fall research course, focusing both on individual motivation and perceptions of the enrichment program as being relevant to real life, supporting autonomy and choice, allowing for active involvement, supporting feelings of belonging, and supporting a focus on learning and growth. Third, we asked whether there were differences in the proportion of students (biology and chemistry majors only) who opted to concentrate in pharmacology, comparing participants in our enrichment program with other biology and chemistry majors at the same institution.

METHOD

Participants

Over 4 yr, all students who took first-year chemistry courses at the private university were invited to participate in a pharmacology-based enrichment program that took place in the Summer after the students' first year in college (the program was tuition-free; however, there was a housing cost to live on campus). The recruitment information highlighted the benefits of participating, including: 1) adding to their resumes that they participated in a National Institutes of Health (NIH)-funded enrichment program, 2) the ability to engage in small-group learning with postdoctoral fellows and graduate students, 3) preparation for future biology and chemistry courses, and 4) preparation for independent study in a biomedical research lab. The research team reviewed the applications and accepted nearly all students who applied to the program each Summer (100% of applicants accepted for cohorts 1, 3, and 4; 97% of applicants accepted for cohort 2).

The program consisted of two parts: 1) a 2-wk Summer minicourse and 2) a research course in the subsequent Fall semester. Over the course of 4 yr, students (n = 58, 71, 64, and 31, respectively) participated in the minicourse. Approximately half of those students in each year were randomly assigned (balanced by demographics such as race and gender) to participate in the Fall research course (n = 28, 34, and 25 students from the first three cohorts). Any student declining to participate in the Fall research course (approximately three to five students each year) was replaced by random assignment by a student with the same demographic profile as the student who declined to participate. Owing to funding limitations, students participating in the fourth year of the minicourse were not given an option to participate in the Fall research component. The demographics of students participating over the 4 yr are shown in Table 1.

The instructional staff for the Summer minicourse and Fall research course included graduate students and postdoctoral fellows in the basic sciences from both the private university and a nearby highly rated research-intensive public university. When choosing the program staff, we selected individuals with content knowledge related to pharmacology (or allied disciplines), some prior teaching experience, and a clear interest in gaining additional teaching experience at the undergraduate level. Additionally, we selected staff with good social and communication skills (e.g., individuals who were enthusiastic, engaged easily in conversation, were able to maintain eye contact, and provided clear oral responses to interview questions). Depending on the number of students attending the program each Summer, eight to 12 instructors were hired each year. The ratio of instructors to students was 1:6 during most small-group work. Of the 36 staff hired over 4 yr, 72% were female and 14% were underrepresented minorities (URMs). The instructional staff provided the daily hour-long interactive lectures in pharmacology, implemented problem-based learning activities, and mentored students to develop hypothetical research projects during the minicourse. In the Fall, a portion of the Summer instructional staff were retained to provide individual

Table 1. Demographics of participants in the pharmacology-based enrichment program[a]

	Summer minicourse (n = 224)	Fall research course (n = 87)
Gender		
Male	34.4%	34.5%
Female	65.6%	65.5%
Race/ethnicity		
African American or black	15.6%	16.1%
Asian, Pacific Islander, or Asian American	42.0%	43.7%
European American, white (not Hispanic), or Caucasian	25.4%	21.8%
Hispanic or Latino/a	9.4%	9.2%
Native American or American Indian	0.0%	0.0%
Multiracial (not URM)	3.1%	3.4%
Multiracial (URM)	4.5%	5.7%

[a]Values represent percentage of program participant sample self-identifying as that category. URM indicates participants who identify as African American or black, Hispanic and Latino/a, or Native American or American Indian.

mentorship to small groups of four to six students engaging in independent research (see detailed description of each of the program components below). The instructional staff received up to a $4000 stipend for participating in the program (those who participated in both the Summer and Fall components received the maximum stipend).

Professional Development for the Instructional Staff

The program directors (faculty members in pharmacology and psychology) delivered professional development to the instructional staff during two full-day workshops preceding the Summer minicourse and one full-day workshop preceding the Fall research course. During the first workshop, the faculty provided examples of how to deliver the lectures in an engaging manner (e.g., by including real-life situations) and how to serve as facilitators in small-group, problem-based learning activities. Best practices in teaching, including the five motivational design principles outlined above, were discussed (see the Supplemental Material for a sample presentation on motivation), and the faculty modeled several aspects of high-quality instruction, with the instructional staff serving as "students." In the second workshop, the faculty reviewed each of the inquiry-based activities and labs in detail. The instructional staff engaged in each of the lab activities together so they would be familiar with the execution, data collection, and statistical analyses. Finally, there was discussion about effective mentorship of small groups engaged in their own hypothetical (minicourse) or actual (Fall research course) research ideas and a review of the motivational design principles.

Program Components

The program consisted of two instructional components: an intensive Summer enrichment minicourse (no course credit) and a self-generated research course (with full course credit) the following Fall.

Summer Minicourse. The Summer minicourse took place on the campus of the private university for 2 wk in May (Monday through Friday, 7 h/d). During the first week, students were introduced to fundamental concepts in pharmacology (see Table 2). In the second week, the drug treatment of four specific diseases was covered. Various learning techniques were used throughout the program, including 1) direct instruction; 2) problem-based and active learning; 3) small-group research and presentations; and 4) short, inquiry-based laboratory experiments. The general daily structure of the minicourse included a 1-h interactive lecture to introduce the concepts, followed by problem-based small-group learning (five to six students per instructor).

One key feature of the minicourse was the inclusion of four inquiry-guided lab activities, each of which focused on one of four drugs: aspirin, caffeine, tobacco, and alcohol. Specifically, the four activities involved the evaluation of 1) the extent to which aspirin partitions into aqueous versus organic solvents as a model of absorption, 2) the effect of caffeine in altering blood pressure and heart rate, 3) whether tobacco extracts can cause DNA mutations in bacteria, and 4) the degree of alcohol intoxication in *Drosophila* (fruit flies) that have two different polymorphisms of the alcohol dehydrogenase (*ADH*) gene. Instead of being required to follow a list of prescribed procedures (i.e., the traditional cookbook-style laboratory), the students designed the lab experiments themselves under the guidance of the course instructors. We have included a sample lab (the alcohol intoxication in fruit flies) in the Supplemental Material. Necessary materials were provided, but the students generated the hypotheses and the experimental design based on their Web-based research and class discussion. During the labs, students also learned how to design and carry out the experiments as pharmacologists would (e.g., constructing a dose–response curve, scoring behavioral observations, being blind to the treatment). Finally, students learned basic information about data analysis and statistics that were appropriate for each experiment.

Another unique aspect of the minicourse included students' development of their own hypothetical research proposal during the 2-wk minicourse. On the first day, students were briefly introduced to the PubMed database and began formulating their ideas about the actions of a drug or toxin of interest to them. We supported student autonomy by giving them the opportunity to explore any topic in pharmacology. Over the 2 wk, students were given time to work individually on the introduction, hypothesis, and experimental design of their proposal, with the guidance of their instructors. On the final day of the minicourse, students participated in a poster session to present their hypothetical research to other instructors and their peers. The poster session was designed to mimic a proposal that one would prepare in graduate school; the session was also designed to prepare students for the Fall research course, during which they would generate and carry out their own real project (described below). Several examples of the hypothetical proposals are listed in Table 3.

In addition to the development of the research proposal and the four inquiry-guided lab activities, there were a

Table 2. Brief overview of syllabus for the Summer minicourse

Overall topic	Specific activities[a]
Week 1: Fundamentals of drug action	
Day 1: Drugs and drug targets	Drug target activity Research: introduction to PubMed Introduction to concept mapping
Day 2: Drug absorption and distribution	PBL: acids, bases, and cocaine addicts Lab: aspirin lab Neuroscience webinar
Day 3: Drug metabolism and excretion	Pharmacokinetics activity PBL: genes and steroids Pen-pal letter writing
Day 4: Dose–response/drug toxicity	Lab: dose–response of caffeine Research: introduction and hypothesis
Day 5: Pharmacogenomics	Lab: ADH flies and alcohol Research: experimental procedures Movie: *Ms. Evers' Boys*
Week 2: Pharmacology and disease	
Day 6: Drug abuse and addiction	Animated neuroscience video Guest speaker on drug addiction
Day 7: Cancer therapies	Lab: nicotine lab Guest speaker on cancer
Day 8: Drugs for obesity	Marketing project Research: design research poster Guest speaker on obesity
Day 9: Drugs for Parkinson's disease	Movie: *Awakenings* Guest speaker on Parkinson's disease
Day 10: Wrap-up	Poster session Pharmacojeopardy Ice cream social

[a]PBL = problem-based learning.

number of other opportunities for active learning. As displayed in Table 2, other activities included the use of two problem-based learning modules, which provided students with the opportunity to work in small groups to carry out online research related to drug absorption and elimination, respectively (a problem-based learning module on the cell biology of steroids has been included in the Supplemental Material). In another activity, students acted out the pharmacokinetic properties of four drugs, including the routes of administration, where and how the drug is metabolized, and how it is excreted. Concept maps, completed by students in small groups, were used as summary activities several times throughout the minicourse to encourage students to organize and synthesize the concepts learned throughout the day, which aligns with the constructivist approach to teaching and learning. Additional activities included movies directly related to pharmacology and four PhD-level seminar speakers who talked about their current research.

Fall Research Course. Students who were randomly assigned to participate in the Fall research course were asked to provide the program faculty with three ideas for an investigation of the effects of a drug or toxin in the treatment of a disease or production of toxicity, respectively. Subsequently, we selected one research idea for each student that could be addressed using one of three types of experimental approaches available in our teaching lab: molecular, cellular, or behavioral (see Table 4 for examples of student research projects using these three approaches). We had already

Table 3. Example of participants' hypothetical research proposals during the Summer minicourse[a]

Blueberries enhance memory by encouraging neurogenesis
Using resveratrol to model the treatment of noise-induced hearing loss in mice
The Use of Dabrafenib to Induce Apoptosis/Senescence in Hairy Cell Leukemia
Increased synaptic connections through the introduction of Pam protein
The use of cibacron blue to inhibit inflammation in mice
Vitamin D supplementation as a treatment for depression in rats

[a]Titles represent students' original wording.

Table 4. Examples of Fall research course participants' project titles, models, and approaches utilized

Approach	Project title[a]	Model
Molecular	Examining the effect of Vitamin E on genes associated with liver cancer in zebrafish	Tumor promoters and polymerase chain reaction
Cellular	The preventative effects of aloe vera on neuromast oxidative damage in zebrafish larvae	Oxygen radical-induced neuronal damage
Behavioral	Effects of chronic caffeine use on learning and memory in adult zebrafish	Learning and memory

[a]Titles represent students' original wording.

developed basic methodological procedures for each of these approaches using zebrafish (both larvae and adults) that students could use as a framework for answering their specific research questions. (These procedures were unrelated to the lab activities during the Summer minicourse.) In several cases, students went beyond the established approaches to develop a new methodology that was better suited to their proposed research project. All students used zebrafish as their model system, as zebrafish are a very useful animal model to test the effects of a drug on a biological response. The short life span and simple treatment paradigm allowed for the use of an animal model in a class-based research course, which would not have been possible with a more complex animal model (e.g., rodents).

During the semester, students with similar research questions were assigned to work in research pods of four to six students. Research pods met one night each week for 4 h. In some cases, students came into the lab on another night to treat their fish or perform an additional experiment. Each student worked on his or her project independently, with guidance from an instructor. At times, students within a research pod also worked collaboratively to develop shared control trials or methodologies that could be used for their individual experiments.

During the first 2 wk of the semester, students spent time learning basics about lab research and then consulted the literature concerning the background for their research idea. With guidance from their instructors, students finalized their research questions and hypotheses and then generated a shopping list of reagents they would need to perform their experiments. Instructors helped students learn the actual techniques and guided them to the literature for reviews about their techniques. At the end of the semester, students prepared final written reports and orally presented their research projects using a conference-style 10-min PowerPoint presentation. All students received both formative and summative feedback on their projects throughout the semester.

Design Principles. Both the Summer minicourse and Fall research course were designed to promote active learning and motivation. The majority of the day during the Summer program was devoted to active learning. As described previously, students engaged in open-guided inquiry in small groups through the four laboratory experiments, two problem-based learning modules, and other small-group activities (e.g., pharmacokinetics activity, concept maps). Active learning was also supported through students' development of their research proposals. While there were a few passive activities (e.g., lecture, guest speakers, movies), all of these activities included components designed to encourage some active learning. For instance, one guest speaker brought genetically modified "transparent" zebrafish that she used in her research, so students could see some of the unique properties of zebrafish. In lecture, the use of think–pair–share occurred frequently to encourage students to actively process the materials being presented. Additionally, the entire Fall research course was an active-learning experience.

Five motivational design principles were incorporated into both the Summer minicourse and the Fall research course. The first design principle, using real-world challenging tasks, was incorporated into the selection of pharmacology as the subject matter. As shown in Table 2, the Summer minicourse centered on real-world applications of basic principles in biology and chemistry, with a specific focus in the second week on the use of drugs to treat common diseases (e.g., obesity, cancer). The focus on pharmacology for the Fall research course also supported application to the real world, as students selected topics of critical importance to society or of personal relevance to investigate.

The second and third design principles, provision of choice (i.e., autonomy support) and encouragement of active involvement, were also key underlying themes in the instructional design of the Summer minicourse and Fall research course. The predominant use of active learning and open-guided inquiry supports students' autonomy, as students are key decision makers in how to proceed with the learning activities. Moreover, student choice was supported by allowing students to select their own research topics related to the research proposal (Summer minicourse) and Fall research. These same activities are, by their very nature, supportive of students' active involvement in learning.

We targeted our fourth design principle, support for feelings of belonging, in a variety of ways. During the Summer minicourse, we set up on-campus housing, so students were housed in adjacent rooms in a single residence hall. We also provided breakfast and lunch for students daily. These social structures afforded the opportunity for informal interactions among students throughout the 2-wk program. Additionally, there were a number of opportunities for small-group work. We varied whether students stayed with the same group (e.g., lab group, research proposal group) or switched groups (e.g., problem-based learning modules, pharmacokinetics activity, concept maps) to support sustained social interactions while also providing the opportunity to interact with a variety of students within the Summer program. During the Fall research course, students worked in small research pods, as described earlier. These pods were an important source of social support, as students often used similar experimental techniques, sometimes even sharing control groups, thus allowing them to problem solve as a team while still carrying out individual research. Finally, we made an effort to select instructors with good social skills, with whom we thought the students could relate. As part of the program, instructors interacted with students during free times (e.g., lunch, breakfast) and shared with the students their pathways into graduate school. In addition, we designated one lunch session during the Summer minicourse for instructors to talk with a group of four to five students about their career pathways.

Our final motivational design principle, use of effort-based evaluation, was focused on students' growth (learning) and understanding, rather than normative performance relative to their peers. To promote a focus on evaluation based on effort and learning, we did not grade the Summer minicourse. Students received informal evaluation about the quality of their work and their effort as they worked in small groups. Additionally, instructors evaluated students' research proposals, developed during the Summer minicourse, through the provision of written, ungraded, feedback throughout the development process. After the poster session in which the research proposals were presented, students received formative feedback on their posters, with a focus on the organization and visual/oral presentation of the poster and on their justification for the study, clarity of the hypotheses, and

connection of hypotheses to the experimental design. Thus, the emphasis of this final formative evaluation of the research proposals was on the overall quality of their work.

In contrast to the Summer minicourse, students received a grade and full course credit for the Fall research course. However, the emphasis was on formative evaluation rather than normative performance. Students completed rough drafts and had the opportunity to revise and improve upon their final papers and proposals before submitting the final version for a grade. Again, the emphasis was on both improvement and the overall quality of students' responses. By providing students with a number of opportunities to revise and develop each portion of their written research project, student effort was emphasized more than normative performance. Moreover, a large portion of the grade was based on students' work during the semester (e.g., designing and carrying out their experiments) rather than on the summative products produced. We provided a grading rubric to the instructors for the research course, which emphasized students' effort (active participation in conducting their research projects, turning in assignments and responding to feedback, etc.), to maintain consistency and fairness in grading among all of the instructors.

Another motivational feature of the Summer miniprogram included a short-term psychological intervention designed to teach students that intelligence can develop and grow with effort (i.e., it is incremental). Students were randomly assigned to either an incremental ability (treatment; modeled after Aronson *et al.*, 2002) or control condition. For the control condition, students watched a webinar developed by one of the authors providing basic neuroscience concepts and the neurobiology of drug abuse and addiction. Students in the incremental condition saw the same webinar, but there was additional information embedded within the webinar demonstrating that hard work can increase the size of brain areas associated with cognition, and hence intelligence. The next day, an exercise was used to reinforce and internalize the message that intelligence is malleable. Students in both the control and incremental conditions were asked to write a letter to an at-risk middle school student about what they learned in the webinar. Students in the incremental ability condition focused their letters on the message that it is possible to overcome challenges and succeed, especially with hard work, to reinforce the message they received during the webinar. Students in the control condition were asked to write about how drugs and alcohol impair brain function.

Practical Considerations

Several features of the program were important in the design and implementation. First, the costs totaled approximately $80,000 per year (not including faculty effort). The major cost categories were stipends to the postdoc and graduate student instructors (up to $4000/instructor), the reagents for the lab research ($10,000–15,000), and costs associated with providing food and housing to participants during the Summer minicourse (~$20,000). Additionally, the faculty members (co–principal investigators) involved with the development, implementation, and evaluation of the program received 15–25% effort for their role; however, it is difficult to separate out the effort specifically related to implementing the program from the other elements (design and evaluation). The majority of students paid for their own housing during the Summer program, although we did provide supplements or full reimbursement for housing for students with moderate to severe financial need.

Evaluation

Knowledge Assessment. Students completed a knowledge assessment (pretest) on the first day of the Summer minicourse. The assessment consisted of multiple-choice questions targeting concepts in biology (11 questions) and chemistry (nine questions). On the final day of the Summer minicourse, a posttest was administered that contained the same questions as the pretest but with the questions reordered. We did not provide students with answers to the pretest after they completed it. However, many concepts presented during the course included the correct answers to the pretest questions. Reliability analyses were not performed, because the individual questions assessing biology or chemistry targeted different concepts. Thus, we would not expect students' responses to all of the biology (or chemistry) questions to be highly correlated. Sample items for knowledge content assessment are as follows.

1. What is the function of the enzyme called a "kinase"?
   a. It increases kinetics of cellular signaling reactions.
   b. It cleaves chemokines.
   c. It moves phosphate groups from one molecular to another.
   d. It generates cyclical AMP.
   e. don't know
2. An acid that does not dissociate completely in water is called:
   a. a strong acid
   b. a weak acid
   c. ionized
   d. hydrophobic
   e. don't know

Students did not receive a grade for either assessment, nor were they told in advance that they would be asked to complete the assessments.

Motivational Beliefs and Program Assessment. To complement findings related to participants' gains in content knowledge, we also assessed the motivational effects of our pharmacology enrichment program (see Tables 5 and 6). All measures displayed adequate internal reliability (indicated by Cronbach's alpha; see Table 5) and model fit (indicated by confirmatory factor analyses) at both time points (after the Summer minicourse and at follow-up).

Participants provided self-reports on their science motivation directly following the Summer minicourse and during their fourth semester in college, approximately o1 mo after completing the Fall research assessment (i.e., follow-up assessment). Motivation was assessed using four well-established measures: interest (Conley, 2012), self-efficacy (Estrada *et al.*, 2011), mastery-approach goal orientation (Midgley *et al.*, 2000), and performance-approach goal orientation (Midgley *et al.*, 2000). These complementary constructs assess different aspects of students' motivation toward science, including their interest in science (interest), confidence in their ability to perform research-related tasks

Table 5. Self-report measures and sample items[a]

Scale	Number of items	Reliability (α)		Sample items
Science motivation		Post–Summer minicourse	Follow-up assessment (sophomore year)	
Interest	4	0.89	0.90	Science is exciting to me.
Self-efficacy	6	0.86	0.90	I am confident that I can use scientific literature and/or reports to guide research.
Mastery-approach goal orientation	5	0.76	0.84	One of my goals in science is to learn as much as I can.
Performance-approach goal orientation	5	0.91	0.90	It's important to me that I look smart compared to others in science.
Incremental beliefs	8	0.94	0.93	No matter who you are, you can significantly change your intelligence level.
Program perceptions		Summer minicourse	Fall research course[b]	
Connection to real life	4/3	0.89	0.86	My [program] instructors relate course material to real life.
Autonomy support	6	0.88	0.85	My [program] instructors listen to how I would like to do things.
Opportunities for involvement	3	0.70	0.67	During [the program] I have opportunities to participate in class discussion.
Feelings of belonging in program	4	0.87	0.91	[Felt] very welcome (1) to NOT very welcome (10)
Instructor is personable	11	0.95	0.96	My [program] instructors are approachable.
Perceived mastery goal structure	7	0.83	0.87	In [this program], trying hard is very important.
Perceived performance goal structure	5	0.90	0.85	In [this program], it's important to do better than other students.

[a]All science motivation and program perception items measured on a five-point Likert-type scale except for "Feelings of belonging in program," which was measured on a 10-point scale, and "Incremental beliefs," which was measured on a 6-point scale. The "Feelings of belonging in program" scale was reverse-coded such that high ratings indicated higher levels of belonging.

[b]Only students who completed the fall research course responded to those items regarding their perceptions of the fall research course.

in science (self-efficacy), focus on developing learning and understanding (mastery-approach goal), and focus on demonstrating competence, or looking smart, in comparison with others (performance-approach goal). Based on the five design principles outlined earlier, our pharmacology enrichment program was designed to increase the first three variables (interest, self-efficacy, mastery goals) but decrease performance-approach goals. Specifically, the focus on real-world challenging tasks that could be completed successfully with effort was designed to enhance interest, mastery goals, and self-efficacy. Autonomy support and active involvement were included to enhance interest and mastery goals, while support for belonging specifically targeted interest. Finally, the use of criterion-based evaluation was included to enhance mastery goals and self-efficacy and to decrease performance-approach goals. We also included a measure of theories of intelligence (Dweck, 1999), which assesses the degree to which individuals view intelligence as fixed or malleable (incremental). This measure served as a manipulation check for the incremental ability condition.

Participants also reported their perceptions of the Summer minicourse and Fall research course. Specifically, seven measures were selected to gauge the extent to which students perceived the Summer minicourse and Fall research course as motivationally supportive. Our first motivational design principle, the use of real-world challenging tasks, was assessed by asking students to report about the connections between the course materials and real life using a measure developed by Linnenbrink-Garcia *et al.* (2013). After the Summer minicourse and Fall research course, we measured our second design principle, perceived provision of choice, using a six-item adaptation of the Learning Climate Questionnaire (Black and Deci, 2000), which assesses autonomy support. Our third design principle, active involvement, was assessed using two slightly different three-item opportunities for involvement scales developed for this study. Our fourth design principle, feelings of belonging, was assessed with two different scales: one focused on students' overall perceptions of belonging during the Summer minicourse and Fall research course (Asher and Weeks, 2014), and the other assessed how personable students perceived the instructors to be (adapted from Linnenbrink-Garcia *et al.*, 2013). Our fifth and final design principle placed an emphasis on effort-based evaluation and de-emphasized competition. To gauge students' perceptions of this design principle, we used two subscales from the Patterns of Adaptive Learning Scales (Midgley *et al.*, 2000), assessing the extent to which participants perceived the program as focused on learning and development (mastery goal structure) or on competition (performance goal structure).

Institutional Records. Students who participated in the pharmacology enrichment program provided us with access to their institutional records. From these records, we identified students' majors and coded them as science related (e.g., biology, neuroscience, biomedical engineering) or non science. We also gathered information about whether

Table 6. Participants' science motivation and program perceptions[a]

	Mean (SD)	% Students agree/strongly agree
Science motivation post–Summer minicourse		
Interest	4.51 (0.52)	91.9
Self-efficacy	3.94 (0.61)	54.3
Mastery-approach goals	4.45 (0.43)	93.0
Performance-approach goals	3.03 (0.91)	21.5
Science motivation at follow-up (Sophomore)		
Interest	4.34 (0.62)	87.9
Self-efficacy	3.89 (0.68)	60.6
Mastery-approach goals	4.27 (0.56)	83.4
Performance-approach goals	2.89 (0.92)	23.8
Summer minicourse program assessment		
Connection to real life	4.08 (0.73)	72.1
Autonomy support	3.98 (0.69)	58.6
Opportunities for involvement	3.98 (0.52)	61.3
Feelings of belonging in program	7.72 (1.53)	75.4
Instructor is personable	4.15 (0.64)	65.1
Perceived mastery goal structure	4.22 (0.55)	71.9
Perceived performance goal structure	2.06 (0.75)	1.1
Fall research course assessment		
Connection to real life	4.01 (0.64)	69.3
Autonomy support	4.25 (0.53)	74.4
Opportunities for involvement	4.62 (0.55)	87.3
Feelings of belonging in program	8.62 (1.06)	95.5
Instructor is personable	4.46 (0.54)	84.8
Perceived mastery goal structure	4.18 (0.53)	69.6
Perceived performance goal structure	2.16 (0.75)	3.8

[a]Values reflect ratings from students in cohorts 1–3 of the program. All constructs measured on a five-point scale; "Feelings of belonging in program" measured on a 10-point scale. Higher scores indicate greater levels of endorsement. "% Students agree/strongly agree" represents students who responded with a 4 or 5 for all scales except for "Feelings of belonging in program" (represents students responding 7 or above). Fall research course assessment consists of responses from students in Fall research course only.

the students elected to concentrate in pharmacology, an option available for students majoring in biology or chemistry. Additionally, we drew from a larger set of deidentified institutional data available to determine the overall proportion of biology and chemistry majors at the same institution who concentrated in pharmacology, subtracting out the number of pharmacology enrichment program participants so we could compare these two groups. To capture final selections on majors and pharmacology concentrations, we report data from students who had recently graduated or were in their senior year (first two cohorts of program participants) as an indication of their persistence in science.

RESULTS

Content Knowledge

To determine the effect of participating in the Summer enrichment program, we assessed students' knowledge of basic biology and chemistry concepts before and after the Summer minicourse for students in all 4 yr of our program. Posttest scores were compared with pretest scores to assess the short-term impact of the Summer program on competence in basic principles of biology and chemistry (Figure 1). It is important to note that students had some limited background knowledge in these fields, having taken high school biology and chemistry. Additionally, all but a few students in our sample took a chemistry course in the first year of college, but many waited until their sophomore year to take the biology core courses. A repeated-measures analysis of variance, with time as a within-subjects factor, indicated that there were statistically significant gains in both biology ($F(1, 219) = 154.94$, $p < 0.0001$) and chemistry ($F(1, 219) = 38.01$, $p < 0.0001$) knowledge. After the Summer minicourse, participants demonstrated an average knowledge gain of 15% in biology and 8% in chemistry, suggesting that the Summer minicourse was effective in enhancing students' knowledge in both biology and chemistry.

Science Motivation and Program Perceptions

Next, we examined participants' science motivation and students' perceptions of the program as motivationally supportive after completing the Summer minicourse and Fall research course. These analyses were conducted for participants in cohorts 1–3 of the program, as data for the follow-up assessment (i.e., 8 mo after the Summer program) had not yet been collected from cohort 4 participants.

Beliefs about Intelligence. We first conducted a manipulation check to determine whether the incremental ability condition enhanced students' beliefs that intelligence is malleable (e.g., incremental, or it can develop and grow), relative to those in the control group. Incremental ability beliefs significantly differed as a function of incremental ability condition both after the Summer minicourse ($F(1, 181) = 33.37$, $p < 0.001$) and at the follow-up assessment ($F(1, 166) = 7.65$, $p = 0.006$). As expected, participants in the incremental ability condition reported higher incremental beliefs (Summer minicourse: M = 4.75, SD = 0.79; follow-up assessment: M = 4.39, SD = 0.87) compared with students in the control condition (Summer minicourse: M = 3.94, SD = 1.06; follow-up assessment: M = 3.99, SD = 1.07).

Science Motivation. To determine whether differences in the within-program conditions (incremental ability, Fall research experience) should be considered or whether we

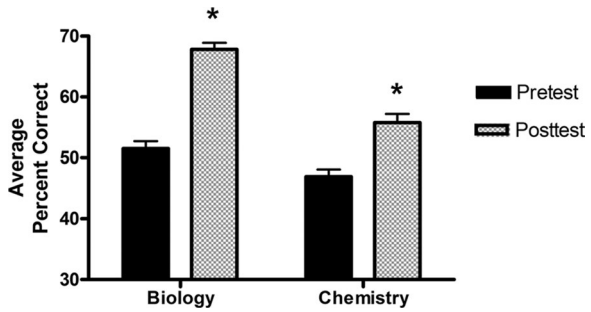

Figure 1. Gains in biology and chemistry content knowledge (±SEM) over the course of the Summer minicourse. Pretest was assessed on the first day of the Summer minicourse; posttest was assessed on the last day of the Summer minicourse. Repeated-measures ANOVAs indicated that pretest and posttest differed significantly for biology and chemistry, *, $p < 0.0001$.

Table 7. MANOVA to test for within-program effects

	Pillai's T	*df*	*p* value
Science motivation post–Summer minicourse			
Incremental versus control	1.93	4, 181	0.11
Science motivation at follow-up (sophomore)			
Incremental versus control	0.89	4, 163	0.47
Fall research course versus none	0.64	4, 163	0.63
Incremental condition × fall research experience condition	0.85	4, 163	0.50
Summer minicourse program assessment			
Incremental versus control	0.97	10, 139	0.47

could collapse across (i.e., combine) conditions for our analyses of student motivation, we tested whether there were significant differences in students' science motivation as a function of the two within-program conditions using two multivariate analyses of variance (MANOVAs). We found no significant differences among the groups as a function of these conditions (see Table 7). Therefore, in our subsequent primary analyses, we collapsed across the two conditions.

Table 6 provides a summary of participants' average ratings of their science motivation and the percentage of students whose average ratings indicated that they agreed or strongly agreed with the items. Immediately following the Summer minicourse and continuing into their sophomore year (i.e., follow-up), on average, program participants reported high levels of interest, self-efficacy, and mastery-approach goals in science. These three forms of motivation were specifically targeted through our motivational design principles and are considered to be beneficial for students' engagement and learning. The findings are particularly pronounced for interest and mastery-approach goals, with 83–93% of participants indicating they agree or strongly agree with the items. Notably, students also reported very low levels of performance-approach goals (e.g., trying to look smart or outperform others), with only around 20–25% of participants agreeing or strongly agreeing with these items. As our pharmacology enrichment program was designed to de-emphasize performance goals, this pattern of findings is aligned with the goals of the program. Taken together, the pattern of results suggests that students participating in any component of our pharmacology enrichment program displayed high levels of adaptive science motivation both after the Summer minicourse and Fall research course components.

Program Perceptions. Table 6 also displays participants' perceptions of a number of key motivational design principles incorporated within the Summer minicourse and the Fall research course. The measures assessing the Summer minicourse perceptions were completed by all students; measures assessing the Fall research course were only completed by students who participated in the Fall research course. Parallel to the analyses for science motivation, we first examined whether there were differences in Summer program perceptions for students in the incremental ability versus control conditions using a one-way (incremental, control) MANOVA. Participants in these two conditions did not significantly differ (see Table 7); thus, we collapsed across the incremental ability condition for the Summer program perception analyses. As the Fall program perceptions were only completed by students who participated in the Fall research experience, we did not test for any differences between conditions for these analyses.

Overall, students' ratings indicate that they perceived both the Summer minicourse and the Fall research course to be motivationally supportive. Across both experiences, students rated connections to real life, autonomy support, opportunities for involvement, feelings of belonging, and mastery goal structure very highly (see Table 6); means ranged from 3.98 to 4.62 (5-point scale) with between 58.6 and 84.8% of the students agreeing or strongly agreeing with the items in these scales. Moreover, given that the pharmacology enrichment program was specifically designed to de-emphasize performance goals, or a focus on demonstrating competence, it is very encouraging that fewer than 4% of students in the Fall research course and 1% in the Summer minicourse reported the course as emphasizing performance goals. Together, these results suggest that participants perceived both the Summer minicourse and Fall research course as motivationally supportive based on our five design principles, which is in keeping with the overall reported high levels of science motivation previously reported.

Selection of Majors

Finally, we examined students' selection of major and decision to concentrate in pharmacology. For these analyses, we focused on students in cohorts 1 and 2. Students in these two cohorts recently graduated or were in their senior year, which allowed us to have more accurate data as students often shift majors and typically do not declare concentrations until later in their college careers.

As expected, a majority (83%) of the pharmacology program participants majored in science (e.g., a biological, chemical, or biomedical field). Because we introduced pharmacology as a subject area to students participating in the program, we were especially interested in whether their participation may have impacted their decision to focus on pharmacology as a subdiscipline. At our university, students who major in biology and chemistry have the option to concentrate in a variety of subdisciplines within the biological and chemical sciences, (e.g., pharmacology, biochemistry, genetics). Of those who participated in the pharmacology-based enrichment program (i.e., those who participated in the minicourse, regardless of their participation in the Fall research course), 53 of the 127 participants majored in biology or chemistry. From this group who had the option of focusing on pharmacology, 26% chose to concentrate in pharmacology. In contrast, only 7% of all biology and chemistry majors (n = 378) during the same two academic years as our participants chose to concentrate in pharmacology. A chi-square test for independence indicated that biology and chemistry students who participated in the pharmacology enrichment program were more likely to concentrate in pharmacology than students who did not participate in the pharmacology enrichment program ($X2$ (1) = 19.09, $p < 0.001$).

We were also interested in determining whether students who participated in both the Summer minicourse and the Fall research course would be more likely to concentrate in

Table 8. Percentage of program participants and nonparticipants concentrating in pharmacology[a]

	Summer minicourse only	Summer minicourse + Fall research course	Non program participants
% Biology/chemistry majors concentrating in pharmacology	18.50	34.60	7.40
Total number of biology/chemistry majors	27	26	378

[a]Numbers represent participants from the first two program years.

pharmacology than students who participated in the Summer minicourse alone. Results from an ancillary chi-square analysis indicated that students who participated in the Summer minicourse only, students who participated in the Summer minicourse plus the Fall research course, and nonparticipants differed in their likelihood to concentrate in pharmacology ($X2$ (2) = 23.00, $p < 0.001$). As displayed in Table 8, program participants in both the Summer minicourse only and Fall research course conditions concentrated in pharmacology more often than students who did not participate in our program. Fall research course participants in particular were likely to concentrate in pharmacology, with more than one-third of biology and chemistry majors concentrating in pharmacology. These ancillary analyses, however, should be interpreted with caution; chi-square tests require that expected sample sizes for each cell be greater than five, an assumption that was violated in this ancillary analysis. A future analysis after the next cohort can be assessed may address this cautious interpretation.

DISCUSSION

Currently, there is a shortage of individuals educated in the United States who are pursuing science careers, leading to a future talent deficit in STEM-related fields (Hawley *et al.*, 2014). One contributing factor to this shortage is that, while many individuals enter college with the intention of pursuing a science-related career, a significant proportion drop the STEM major for a variety of reasons (PCAST, 2012; Chen, 2013). In an attempt to address this shortage, we developed a pharmacology enrichment program designed to increase students' biology and chemistry knowledge, science motivation, and, ultimately, increase the number of students studying pharmacology. In this paper, we provide a rich description of our pharmacology enrichment program, detailing how we utilized active learning and five motivational design principles that are based in educational and psychological theory and research to create a Summer minicourse and Fall research course. Overall, our evaluation of the program suggests that it was beneficial in terms of supporting 1) increases in students' biology and chemistry content knowledge, 2) high levels of adaptive science motivation, and 3) decisions to major in biology or chemistry and to concentrate in pharmacology. Below, we highlight several key lessons learned and consider implications for practice and future research.

A key strength of our approach was the integration of research teams trained in both the basic sciences (pharmacology) and educational psychology. With this background, we were able to develop an engaging Summer minicourse and Fall research course that not only supported students' learning but also their science motivation and subsequent persistence in science throughout college. Thus, an important lesson learned from our approach is the need for multidisciplinary teams consisting of content experts and experts on student learning and engagement when designing educational enrichment programs. Building from this expertise, we identified several key elements of our pharmacology enrichment program.

First, the inclusion of active learning was critical for supporting students' learning and motivation. Instead of providing traditional lectures, we implemented various active-learning methods (e.g., think–pair–share) during the lecture period to engage the students. In addition, problem-based learning activities were used to reinforce concepts learned during the lecture. Active learning is often discussed in the context of precollege education; however, some studies illustrate that active learning is also useful in undergraduate and graduate pharmacology-based courses. For instance, active learning in pharmacology-related topics has resulted in improvement in student understanding when used with nursing students (Kaylor, 2014), medical students (Zgheib *et al.*, 2010), and PharmD (doctor of pharmacy) students (Satyanarayanajois, 2010). Among undergraduates enrolled in STEM courses, a recent meta-analysis comparing active learning with traditional lecturing also provides evidence of the benefits of active learning (Freeman *et al.*, 2014). Thus, our results highlighting the gains in student knowledge and motivation as a result of participating in our pharmacology Summer minicourse are in keeping with prior research in which educators use active learning in the context of pharmacology instruction and among undergraduate populations in STEM.

Second, the use of five motivational design principles appeared effective in terms of students' overall levels of motivation, perceptions of the Summer program, and decisions to major in biology or chemistry and to concentrate in pharmacology. The use of these motivational design principles in relation to a pharmacology enrichment program is particularly novel. While many STEM enrichment programs seek to enhance psychological variables such as interest or self-efficacy (e.g., Bakken *et al.*, 2010), very few work directly with motivational researchers to embed research-based design elements that target multiple forms of motivation simultaneously. For our program, we drew from decades of empirical research and motivational theory (e.g., Turner *et al.*, 2011; Linnenbrink-Garcia *et al.*, 2013) to identify and implement five motivational design principles: 1) inclusion of real-world challenging tasks, 2) provision of choice surrounding academic tasks, 3) encouragement of active involvement, 4) support for feelings of belonging, and 5) use of effort-based evaluation) to support science self-efficacy, science interest, and a focus on learning and understanding (i.e., mastery goal). We describe how these principles were embedded in both the Summer minicourse and Fall research course and then provide evidence, based on students' perceptions of both

components of our program, that our efforts to implement the designed principles were effective. We encourage others interested in addressing the leaky pipeline in STEM fields to take a similar approach. These five motivational design principles can be readily applied to a variety of fields of study and programs.

Notably, we also included a short-term psychological intervention (e.g., Yeager and Walton, 2011) designed to encourage program participants to endorse the belief that intelligence is malleable rather than fixed. Although the benefits of incremental ability beliefs is well documented (Yeager and Dweck, 2012), we found no added benefit for students randomly assigned to the incremental ability condition in terms of students' science motivation either immediately after the Summer minicourse or 8 mo later (after the Fall research course). Future analyses over the next several years will determine whether there is a long-term benefit of the incremental ability exercise on science motivation.

Another important design element in our pharmacology enrichment program was the inclusion of an early independent research experience (e.g., Fall research course). We chose to implement the early research experience as a "best practice" in undergraduate science education. Authentic research experiences for undergraduates have been shown to improve science interest and student engagement (Seymour *et al.*, 2004; Frantz *et al.*, 2006; Lopatto, 2007; Harrison *et al.*, 2011; Eagan *et al.*, 2013). Additionally, retrospective research suggests that early research experiences often lead to an increase in interest in science careers and pursuit of a PhD (Russell *et al.*, 2007). Most research experiences occur later in the undergraduate career (during students' third and fourth years); however, the report from PCAST (2012) recommends engaging students in research courses and research programs in the first 2 yr of college. Early research experiences are expected to increase students' positive attitudes toward science and decrease attrition in STEM fields (Nagda *et al.*, 1998; Russell *et al.*, 2007; Carter *et al.*, 2009). Authentic research experiences for undergraduate students typically consist of participation in an ongoing project in a laboratory of their choice. In our pharmacology enrichment program, the authentic research experience was actually self-generated from individual interest and carried out in our teaching lab, not in the lab of a specific faculty member. Our ancillary analyses examining the percentage of students concentrating in pharmacology provide some evidence for the effectiveness of these types of self-generated research experiences for supporting students' persistence in science, particularly in pharmacology. Surprisingly, however, students who participated in the Fall research course in addition to the Summer minicourse did not significantly differ from those who did the Summer minicourse alone in terms of their science motivation. However, future analyses will inform us whether the Fall research course can significantly enhance the effects of the Summer enrichment experience on science persistence over longer time periods.

In closing, we provide proof of concept that it is possible to develop and implement a pharmacology-based enrichment program building from current research in both education and psychology. Moreover, our results provide initial support for the benefits of taking this approach. We found statistically significant increases in biology and chemistry knowledge and a significantly greater proportion of students participating in our enrichment program concentrated in pharmacology several years later. We also documented overall high levels of adaptive forms of science motivation (self-efficacy, interest, mastery goals) and provided evidence that students did indeed perceive the pharmacology enrichment program as aligned with our motivational design principles. Given these encouraging findings, we urge educators to consider incorporating into their classrooms/labs active learning and the five motivational design principles presented here that support students' learning and science motivation.

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Supplemental Material

CBE—Life Sciences Education

Godin *et al.*

Supplemental Material

CBE- Life Sciences Education

Godin et al.

Table of Contents

What is motivation?

- Based on an individual's beliefs about:
  1) Can I do this?
     - **Perceived competence** (self-efficacy)

  2) Why do I want to do this?
     - **Intrinsic**: engage for enjoyment, task is valuable/interesting, to learn or improve
     - **Extrinsic**: engage to get a reward, avoid punishment, impress others, outperform others

How is the summer program designed to support motivation?

- Real-world, challenging tasks
- Self-generated academic work
- Active involvement in learning
- Supports feelings of belonging
- Informal, effort-based evaluation

Supporting Perceived Competence

GOAL: Want students to feel like they can learn science (biology, chemistry, pharmacology)

TIPS :

- Hold high but realistic expectations (remember these are undergrads with limited science background)
- Support students to successfully solve challenging problems/answer questions on their own
- If students are not successful, help them to see other approaches that might lead to success in the future

Supporting Intrinsic Motivation

GOAL: Want students to enjoy science, focus on learning and understanding

TIPS: Support autonomy

- Provide explanations, rationales
- Allow students to make choices
- Be patient, give students time to work through activities on their own

TIPS: Make learning meaningful

- Make connections between course materials and real life
- Actively involve students in learning

Supporting Intrinsic Motivation

GOAL: Want students to enjoy science, focus on learning and understanding

TIPS: Support Feelings of Belonging

- Help students relate to you
- Foster positive relationships among LEAP students
- Encourage atmosphere of respect and warmth

TIPS: Focus Evaluation on Learning, Improvement

- Provide private feedback focused on the process (not the product)
- View mistakes an opportunity for learning

Reducing Extrinsic Motivation

GOAL: Do NOT want students to focus on outperforming others, getting good grades, demonstrating competence

TIPS: Reduce competition

- AVOID directly comparing students or pointing out particular students as smart
- AVOID activities that support competition or social comparison among students

TIPS: Reduce controlling behaviors

- AVOID being overly directive (instead support autonomy)
- Do NOT use rewards, prizes, etc.

Bar Flies: Pharmacogenetics of Ethanol Metabolism

Objectives:

1) Describe the metabolism of alcohol.
2) Describe how a gene polymorphism in ADH can increase the risk of alcohol addiction
3) Explain how a gene mutation can affect protein levels vs protein structure
4) Discuss how to convert observation data (qualitative) into quantitative data for analysis
5) Explain the basic use of an ANOVA for statistical analysis

Background:

Several types of gene variations can influence alcohol intoxication (rate and extent) in people, leading to different risks of the development of alcoholism. Such gene variations can be studied in animal or organism models of disease. The *Drosophila melanogaster* is an excellent model for studying the behavioral effects of alcohol, based on the work of Ulrike Heberlein* at the University of California at San Francisco. Like people, the flies possess the alcohol dehydrogenase (ADH) gene, which controls the production of the major alcohol oxidizing enzyme, ADH. Flies are attracted to alcohol to get their food, but at higher concentrations of alcohol they become intoxicated and can even die of alcohol poisoning. Thus, having a functional ADH enzyme serves as a survival mechanism.

Behavioral activity during intoxication (summarized by Ogueta eta l., 2010):
In fruit flies, intoxication causes initial hyperactivity followed by the flies becoming increasingly uncoordinated and sedated. As brain and hemolymph ethanol concentrations increase, the flies lose their ability to control posture when challenged, and after long exposure lose control over walking and flying movements. Inebriated adult flies also show an increase of courtship activity.

There are several isoforms of the human ADH gene that affect the rate and extent of alcohol oxidation. The same is true in Drosophila. Some have an allele mutation in their ADH gene leading to flies with null or greatly reduced ADH activity ("ADH minus" flies). These flies become easily intoxicated by alcohol (like humans!) and can ultimately die of alcohol poisoning.

Flies possessing a functional ADH gene have the ability to oxidize ethanol to acetaldehyde:

$$NAD^+ + ADH + alcohol \text{ --------> } NADH + acetaldehyde + H^+$$

In this activity, students will develop a laboratory experiment comparing the rate and extent of alcohol-induced intoxication in normal ("wild-type") flies and ADH- flies with the ADH gene mutation. Students will rate the fly behavior (blind to the treatment condition) at different times after coming up with a scoring scale for intoxication. After deciding on a specific time-point to compare the effects of alcohol on both types of flies, they will use a statistical analysis (ANOVA) to determine significant differences for main effects of alcohol treatment and polymorphism and interactions at specific doses.

Note to instructors: Before starting the activity review the basics of alcohol oxidation.

$$\text{Alcohol} + NAD^+ \xrightarrow{\text{ADH}} \text{acetaldehyde} + NADH + H^+$$

$$\text{acetaldehyde} + NAD^+ \xrightarrow{\text{AldDH}} \text{acetic acid} + NADH + H^+$$

1. Why are enzymes so important to make biological reactions go?
2. What other kinds of diseases (other than alcoholism) are the result of enzyme deficiencies in the body?

Materials:

Fruit flies (*Drosophila) ADH- and ADH+* (40 of each per student group)
Fly vials and sponges (8 per group)
Alcohol - White wine or 95% ethanol
cotton balls (32 per group)
stirring rods (8 per group)
pipettes
small (10 ml) graduated cylinders
delicate paint brushes
ice bucket

Prior to the experiment, tell students that fruit flies are attracted to alcohol, which is normally made in food that is decaying. If the alcohol is high enough concentration, the flies can get intoxicated.

Discuss with them that fruit flies are a great genetic model for many disorders in humans.
Ask students: "How would you test for alcohol intoxication in fruit flies that have polymorphisms in an enzyme that oxidizes alcohol? What would happen to flies that can't oxidize alcohol?"

Guide the students to design a procedure to answer these questions. Things they will need to find out are:

- The enzyme that oxidizes alcohol
- What kind of polymorphisms exist for this enzyme (ADH) in flies
- How the oxidation of alcohol by ADH proceeds
- Why would a fly have ADH?
- What is a toxic dose of alcohol for a fly?

Students should come up with a control condition (water) and 3 doses of alcohol (white wine is 13%, but can make a higher concentration by adding 95% ethanol). Guide them to come up with a list of conditions similar to the one shown below.

ADH- flies, water	ADH+ flies, water
ADH- flies, alcohol-dose 1	ADH+ flies, alcohol-dose 1
ADH- flies, alcohol-dose 2	ADH+ flies, alcohol-dose 2
ADH- flies, alcohol-dose 3	ADH+ flies, alcohol-dose 3

Then, students should discuss how they will observe and record their data. They should construct a behavioral rating scale for their observations. Here's an example (the whole class should use the same scale).

Behavior score	Behavior
1	Flying around
2	Some movement
3	Little movement
4	No movement but alive
5	Dead

Next, they should make a class decision on a proper data table for recording all their data for their 5 flies at specific time points over 24 hours. Instructor should construct the table on the computer (with projection) and when it is finalized, the instructor should print out enough copies for each student.

A table could look something like this:

Condition Code:_____

Time after exposure	Behavior Score				
	"1"	"2"	"3"	"4"	"5"
15 min					
30 min					
60 min					
2 hours					
4 hours					
8 hours					
24 hours					

Procedure:

Instructors:

For each lab room: Presort flies into an ADH+ vial and an ADH- vial. These flies can be anesthetized when class starts by chilling them on ice for 5-10 minutes. Keeping them on ice afterwards also slows their revival.

1. Give each group 8 empty vials, about 32 cotton balls and 8 stirring rods.

2. Using the stir rod, wedge 3-4 cotton balls in the bottom of each vial.

3. Each student chooses one of the experimental conditions to set up and labels the tube with a piece of tape with their name and the condition (e.g., ADH-, water)
   (Note: later on the instructors will remove the tape and code the vials (A, B, C, etc.) so that the students are "blind" to the treatment condition)

4. Students add 5 mls of either water or varying concentrations of alcohol (white wine or 95% ethanol) to their vials. Each cotton ball should be soaked but not submerged. Using the stirring rod, tap down the cotton balls to wedge them in place and then drain off excess fluid into a beaker or paper towels. They can test the cotton ball's security by inverting the vial.

   Note: Make sure the cotton ball is well-drained, so as not to drown the flies. The cotton ball should be very damp, but not leak liquid when pressed.

5. Dry the inside walls of the vials if they are wet. (Flies can drown in drops of fluid)

6. Give your group the 2 vials of ADH +/- anesthetized flies. The flies in the vial should not be moving. If the flies wings or legs appear to trembling they should be put on ice longer. As soon as the flies warm up, they will wake up and fly away.

7. Open the chilled vial and pour the flies onto a piece of paper. Using the paintbrush, gently sweep 5 flies of one strain to put into each of the labeled vials. Stopper the vial, but leave the vial on its side so the anesthetized flies will not drown in the wet cotton.

8. When the flies revive, turn the vial upright. If less than 3 flies recover, obtain more to make 5 total.

9. The instructor should replace the tape on each vial with a new piece of tape with a code: A, B, C, D, etc. Store the code for the original labels in a notebook. Students should discuss the advantage of being "blind" to the treatment condition (i.e., to eliminate bias when gathering observational data).

10. Return vials to the students – make sure that they don't know which condition they will be observing.

11. Students start their observations and record their behavior over the next 24-hours at the time points that they decided to use.

12. Students should share their data with the other members of their lab and decide which time point they want to use for the data analysis. This should be a time point at which they have a good indication of intoxication. They should also determine what score they will use as having reached "intoxication" (e.g., score of at least 3). They should email you the time point and score that they have chosen as a group that will be used for the data analysis.

13. During the next class, compile the data to show as a table or plot. Then perform the appropriate statistics.

    One way to turn qualitative data into quantitative data is to plot the individual scores as a scatterplot at the agreed-upon time point on a graph with all the doses and both ADH polymorphisms. Put a circle or an X for each fly in each condition. They can draw a line for the median. Note: some believe using a mean for scored data as an average is not appropriate, but this opinion varies widely.

    The data can be analyzed with an ANOVA and a post-hoc test such as Sheffe's test to compare the behaviors of the ADH + vs ADH - flies. (Ideally, non-parametric statistics would be best for scaled data, but this is beyond our discussion today).

14. Have students run the ANOVA and Sheffe's test using the Stats program of choice (Prism).

15. Have a discussion on data analysis, to compare data within and between the different groups. Students need to be sure to differentiate fly death due to alcohol poisoning versus death due to other factors (e.g., poor handling, etc.)

16. Ask students to extrapolate their results to humans; people with highly functioning ADH metabolize alcohol well and have less intoxication, while people with the gene that makes a poorly functioning ADH (or no ADH) are likely to become very intoxicated since they can't get metabolize alcohol very quickly.

By Karen Hopkin

PROFILE

Drunken *Drosophila*

Ulrike Heberlein started out studying fruit fly eyes. So how did she end up inventing the inebriometer?

It began with a simple observation in 1993. Ulrike Heberlein – then an investigator at the Ernest Gallo Clinic and Research Center at the University of California, San Francisco – placed a fruit fly in a little chamber, gave it a puff of alcohol vapor, and monitored its reaction. "What we observed is that a fly behaves just like any other organism when under the influence of alcohol," she says. "First thing it does is become really excited. It runs around really quickly and starts bumping into things." Keep the alcohol coming, and inebriated flies grow increasingly uncoordinated. "Eventually they just sort of fall over and lie there," says Heberlein. Recovery from a binge is no prettier. "They get up, they fall down again. You just observe these tiny little flies and you can relate to them," she says. "You think, this is awfully similar to something that maybe I experienced once in my life."

In the years that followed, Heberlein, now a professor at UCSF, turned those sympathetic observations into a career of studying the effects of drugs and alcohol on fruit flies. She and her colleagues have discovered a handful of genes that influence how these creatures respond to ethanol and cocaine, and they hope that their findings will lead to a better understanding of intoxication and addiction in more complex organisms, including humans. "I think she's more motivated than a lot of basic scientists by a desire to do something medically significant," says Cori Bargmann, a Howard Hughes Medical Institute (HHMI) investigator at the Rockefeller University. "Her project is based on a real conviction that alcohol and drug abuse is a human tragedy and [that] people should do something about it."

From the Zambezi to Berkeley

Heberlein didn't set out to devote her life to drunken *Drosophila*, or even to science. Although she studied biochemistry as an undergraduate in Chile – an experience she imagined would teach her "how life works at a molecular level" – Heberlein was leaning toward pursuing a life of ▸

outdoor adventure. "I did river rafting and mountain climbing for a couple of years in the early 80s," she says. But just as she was about to pack her bags for Zimbabwe to help her boyfriend run a rafting operation on the Zambezi River, Heberlein says, "I realized that maybe going back to science wasn't a bad idea. At least in science I knew what I was doing."

That realization brought Heberlein to Berkeley in 1983, to the laboratory of HHMI investigator Robert Tjian. For her thesis project, Heberlein was searching for the transcription factors that bind to the promoter of one of the few fly genes that investigators had identified: alcohol dehydrogenase. Along the way, she worked out the first cell-free transcription system using fruit fly embryos at different stages of development. "Believe it or not, the *Drosophila* field was well covered genetically, but virtually nobody did biochemistry," says Tjian. "Ulrike really cracked open the entire transcription system in *Drosophila*, which has been paying dividends ever since."

The time in Tjian's lab gave Heberlein "a very solid education in biochemistry," she says. But it also awakened in her a longing to manipulate genes in an animal. Working with isolated bits of DNA and purified proteins in a test tube, she says, "I felt like I had a little too much control over what was happening. And I thought that if I worked with a whole organism, and used genetics rather than pipetting to change conditions, that ultimately I would learn something about what's important to the organism."

In 1988, this desire to learn a genetic approach drove Heberlein across the hall for a postdoc in Gerry Rubin's lab, where she began to study the development of the fly eye. "It's this incredibly precise, beautifully structured compound eye, with 800 units that are aligned almost like a crystal," she says. Heberlein learned the techniques that would allow her to probe the genes that initiate the wave of differentiation that sweeps across the developing eye. She was again breaking new ground experimentally and biologically.

"Ulrike has a history of initiating interesting fields," says Jay Hirsh of the University of Virginia in Charlottesville. "I think she was one of the first to get into the whole question of what causes movement of the morphogenetic furrow during eye development in the fly," he says. "This has become a huge field unto itself."

Like Flies to ... Alcohol

After her postdoc, Heberlein needed to find a job. She learned of an opening at the Gallo center, which had been established to study the effects of alcohol and drugs of abuse on the brain. Heberlein wrote to then-director Ivan Diamond and described her interest in the position. "I said I had studied alcohol dehydrogenase as a graduate student, which made me sound like I knew something about the field, although I really didn't at all," she recalls. Diamond was receptive, but asked Heberlein to outline something more specific. "So I started reading and thinking about how you can measure behaviors induced by alcohol in flies," says Heberlein. "I wrote a two-page proposal. Next thing, I had a job interview, and then I had a job."

> "After the cheapdate paper, flies and alcohol were no longer a laughing matter."
> —*Adrian Rothenfluh*

Launching her career in 1993 at the Gallo, her friends and colleagues say, was a curse and a blessing. "It wasn't exactly the easiest place for a young researcher to get going," says Tjian. The Gallo is physically isolated, located across the Bay Bridge in Emeryville, rather than on the UCSF campus, which he says made it more challenging for Heberlein to recruit talented graduate students and postdocs to aid in her pioneering work.

On the other hand, says Bargmann, the Gallo was willing to support studies that weren't ready for prime NIH funding. "Ulrike's work got started at a point where the whole thing just seemed too wacky for words," she says. "But it's those early times when people think you're crazy that somebody has to step up and support you." The Gallos, who'd donated a portion of their winery profits to address some of the problems associated with alcohol abuse, were willing to give Heberlein that support.

Funding in hand, Heberlein needed to develop a screen that would allow her to tease out the genes that control how a fly responds to alcohol. Enter the inebriometer. The device is a tall cylindrical column, lined with slanted platforms, through which alcohol vapors can be circulated. Flies are placed at the top of the apparatus and, as they become inebriated, lose their footing and tumble to the bottom. Flies fall faster the more sensitive they are to the effects of alcohol. Using the inebriometer, which she built from scratch, Heberlein isolated mutants that are either more sensitive or less sensitive to intoxication than are wild type flies.

"I remember how the audience chuckled, half amused, half bemused," when Heberlein discussed her inebriation assay at a fly meeting in 1998, says postdoc Adrian Rothenfluh. That changed the following year, though, when Heberlein and her team isolated *cheapdate*, a mutation that lowered flies' resistance to the intoxicating effects of alcohol. "After the cheapdate paper, flies and alcohol were no longer a laughing matter," says Rothenfluh.

Cheapdate, cAMP, and Memory

Cheapdate disrupts a peptide called amnesiac, which Chip Quinn's lab at Massachusetts Institute of Technology had previously identified. Amnesiac is involved in learning and memory, reinforcing the theory (proposed by others in the field) that addiction might be a maladaptive form of learning. Heberlein and her colleagues are still trying to identify the receptor to which the neuropeptide binds. They have learned that cheapdate activates cAMP signal transduction in a subset of fly neurons; the same cAMP pathway has been implicated in mediating alcohol's effects in mammals. "So we think we're barking up the right tree," says Heberlein.

The approach was a gamble, says UCSF colleague Cynthia Kenyon. "Going in, it wasn't clear whether she could find single genes that would produce specific effects instead of just a jumble. Or maybe there would have been nothing there to study," she says. Heberlein's experimental rigor

allowed her to find specific genes and to follow through and determine their functions, says Tijan. "Cloning a gene might be easy. But you then have to go and actually figure out what the heck it does."

Although the connection with learning was a surprise, the discovery highlights "why flies are great for this kind of study," says Linus Tsai, Heberlein's former MD-PhD student. "With flies you can do an unbiased search for genes and molecules that might be involved in drug response. You're not limited to what's already known."

Heberlein and her colleagues continue to push those limits, expanding their studies to include cocaine, nicotine, and other drugs of abuse. "We throw everything we can get our hands on at these flies," she says, and additional genes have emerged. For example, Heberlein, Tsai, and other lab members have conducted cocaine sensitivity studies, which have turned up lmo, a tiny little protein expressed in a set of circadian pacemaker cells. These neurons help coordinate various rhythmic behaviors, including locomotion, an activity that goes awry when flies are exposed to cocaine.

Alongside the fly studies, Heberlein is working on proving that the corresponding genes play a role in drug response in mice. "It was a bit of an extrapolation to believe that flies would be a good model to study addiction," says Heberlein. "A lot of people questioned whether that was the right way to go." But the approach, which Heberlein likens to jumping off a cliff, "has really paid off," she says. In addition to the cAMP connection, Heberlein has evidence that lmo is also involved in cocaine sensitivity in mice.

Perhaps, given Heberlein's penchant for adventure, the cliff-diving method should come as no surprise. "Bold and daring things appeal to her," says Bargmann. Tijan agrees: "Ulrike ... takes risks. She goes for the throat. She tries things that other people haven't tried. She's a very strong person. You have to be to start something that other people think is bound to fail."

"I really admire where the work has gone," adds Bargmann. "It probably isn't even zany anymore. Which is too bad." ■

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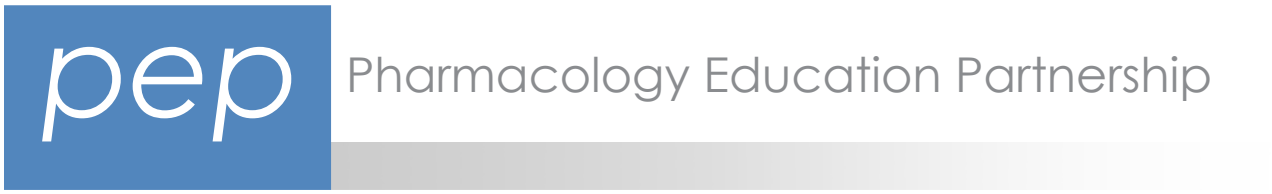


This problem-based learning module includes the following:

- Description of the module
- Learning objectives
- Student Handout (the "problem" handed out to students)
- Content (contains the answers to the problem; handed out after students found their own answers)
- Glossary
- Resources

This module, along with 5 additional ones, can be found at:
www.thepepproject.net

Steroids and athletes: Genes work overtime

Description of the module

The use of steroids by athletes (and body builders) is common and it presents serious health risks. Despite the potential disqualification of athletes for using steroids before or during competition, athletes continue to use them. They must feel that the advantage of enhanced performance is worth the risk of being disqualified. In this module we explore the mechanism by which steroids promote muscle growth. They are notorious regulators of gene transcription, resulting in the synthesis of muscle proteins. Athletes who use steroids try to outwit the drug-testing "police," but, often, they fail the drug test. In this module, we highlight why steroids can persist in the body long after the person stops using the drug.

Learning objectives

1. Understand what is a steroid
2. Understand the definition of 'anabolic' and 'androgenic'
3. Understand the concept of a lipophilic molecule
4. Understand the difference between passive and facilitated diffusion
5. Understand the concept of hormone receptors and where in a cell they are located
6. Understand how proteins pass through a nuclear membrane
7. Be able to describe the structure of DNA
8. Understand the process of gene transcription, how it can be "turned on"
9. Understand the process of protein synthesis
10. Be able to identify parts of a muscle cell; understand how muscle contraction occurs
11. Understand the role of the liver and the kidney in eliminating compounds from the body

This module integrates information from the following areas:

cell biology, endocrinology, chemistry, physiology, sociology, sports

Student Handout

It's fairly common knowledge that exercising a muscle makes the muscle grow and become stronger. However, athletes in the US as well as in many other countries try to enhance their muscle performance even more by using steroids. Similarly, body builders use steroids to make their muscles grow beyond the size that would be produced naturally by lifting weights. How does this actually happen, and what are the consequences?

Let's explore the biology of steroids. Steroids are compounds that are synthesized in the body from the precursor, cholesterol. Some steroids are made in the adrenal glands (near the kidney) and some are made in the sex glands of both males and females.

1. Give an example of a steroid found in the adrenal glands and in the male and female sex glands.

2. Which of these steroids is used by athletes and by body builders?

3. What is an anabolic steroid?

Although anabolic steroids are used to increase muscle growth (and enhance performance), they do a lot of other things in the body as well. In fact, all anabolic steroids have androgenic properties, despite claims to the contrary. For this reason, they are termed anabolic-androgenic steroids or AAS, although most people just say "anabolic steroids" as a shortcut.

4. What is an androgen?

5. List 3 common androgenic effects of anabolic steroids in the body.

When athletes use anabolic steroids to enhance their performance, they don't just take a pill or an injection before the race or before the game. They must use the drug over a period of time in order to obtain the muscle growth. To understand why this is the case, we need to know how steroids actually make the muscles grow. First, after taking an anabolic steroid (by mouth or by injection), the steroid enters the bloodstream and travels to all tissues in the body (see Module 1). Most anabolic steroids are very lipophilic, and therefore, they can cross cell membranes easily to reach the inside of all cells.

6. Define "lipophilic." What characteristic of the steroid structure makes it lipophilic?

7. Why can a lipophilic steroid cross cell membranes so easily?

Once inside the cell, the steroid binds to a special protein called a steroid receptor. In this case we are referring to the "androgen receptor." The complex containing the anabolic-androgenic steroid and its receptor then travels through the cytoplasm and crosses the nuclear membrane to enter the nucleus.

8. How does a big, bulky molecule consisting of a steroid and a protein get across a nuclear membrane?

Once in the nucleus, the steroid receptor complex comes into contact with the DNA. The steroid receptor binds to a specific site on the DNA molecule, causing the DNA to start the process of gene transcription. This leads to the synthesis of certain proteins, depending on the cell-type and the part of the DNA to which the steroid receptor complex binds. All of these events take time, and a sustained use of the steroid is required to continually instruct the genes to synthesize more protein.

9. What kind of molecule is DNA? Describe its essential features.

10. What is gene transcription?

11. How is the protein synthesized?

The cell-type that contains the androgen receptor will define the kind of protein that is synthesized. For example, in the case of the muscle cell, the anabolic steroid will stimulate the synthesis of certain types of muscle fiber proteins.

12. In what type of cells would anabolic-androgenic steroids act to cause:
    - the growth of chest hair
    - acne
    - emotional disturbances such as aggression

As more muscle fiber proteins are produced, the muscle gets bigger and more powerful. But once the athlete or body builder stops taking the steroids, their muscles slowly revert to their normal size.

13. Draw a muscle cell. Label the essential structures in the muscle cell that help it to contract. Which muscle proteins constitute the muscle fibers?

The use of the steroids provides an unfair advantage over non-drug using athletes. So steroids have been banned from use in local, national and international competition. Despite this rule, many athletes continue to use steroids until shortly before a competition, when they hope that a drug test will not detect it. In many cases, this plan doesn't work. The drug is still present in their bodies long after the athlete stops taking it. This is due to the lipophilic character of the steroid.

Lipophilic compounds are difficult to eliminate from the body (the same is true for THC, found in marijuana). Normally, drugs are eliminated by the liver and the kidney. Enzymes in the liver convert (metabolize) drugs into a more water-soluble (polar) form. Once the drug is in a more water-soluble form, it travels through the bloodstream to the kidney, where it is collected in the urine and eliminated from the body. But in the case of highly lipophilic drugs such as anabolic steroids, they are metabolized very slowly so that only small amounts of drug are eliminated over time.

14. Why is it so difficult for an anabolic steroid to be metabolized by the liver enzymes?

15. Why is it so difficult for an anabolic steroid to be retained by the kidney where it would be eliminated in the urine?

If the lipophilic steroid can't be metabolized easily nor retained by the kidney, then it re-enters the bloodsteam to circulate throughout the body. However, it does like to "hide" in cells that contain a lot of lipids, such as fat cells. With continued use, the anabolic steroid starts to accumulate in the fat cells.

16. If the athlete stops using the steroid, the amount of steroid in the blood starts to decrease. What would account for the initial decrease of steroid in the blood?

17. Although the steroid decreases in the blood, it doesn't disappear right away. Instead, there is a steady low-level amount of steroid that is present in the blood over a long period of time (and thus the positive drug test). Where is the steroid coming from? What is the major force moving it into the bloodstream?

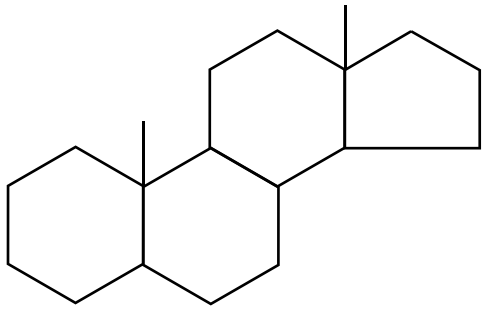
The ban on steroid use in sports is not based solely on the unfairness issue. There are serious health consequences that can occur from long-term steroid use.

18. List 3 additional health consequences from the repeated use of anabolic steroids.

The biochemistry of steroids

Steroids are a class of **hormones** that are synthesized by specific cells or tissues in the body and released into the bloodstream. Steroids are **non-polar** molecules produced from the precursor cholesterol. Four interconnected rings of carbon atoms form the skeleton of all steroids (**Figure 1**). The type of steroid formed is dependent upon the **polar** hydroxyl groups (OH) attached to the interconnected rings and the synthesizing tissue. Examples of synthesizing tissues, the corresponding steroids and some of their many functions are listed below.

Adrenal gland	glucocorticoids (cortisol)	maintain blood glucose during stress, anti-inflammatory
	mineralocorticoids (aldosterone)	regulate kidney function (water retention)
Ovaries	estrogen	promotes endometrial cell (uterine) proliferation
	progesterone	promotes endometrial cell differentiation
Testes	testosterone	stimulates sperm production promotes muscle growth



General steroid structure

Figure 1. The general structure of a steroid molecule is shown. Different steroids are defined by the location of polar hydroxyl groups (OH) attached to the C atoms within the rings.

Most steroids are used for medicinal purposes, especially the glucocorticoids, which are powerful anti-inflammatory agents. However, due to very serious side effects from long-term use (such as weight gain, bone density loss, increase in blood cholesterol levels, and liver disorders), they are only used as a last resort. Estrogen and progesterone are used in birth control pills and also in post-menopausal women to replace what is lost during aging (this is controversial). Testosterone (**Figure 2**) is an **anabolic steroid**, which promotes growth of muscle tissue. "Anabolic" literally means to build up tissue and it refers to the retention of nitrogen atoms in the body reflecting an increase in protein synthesis and/or a decrease in protein breakdown. While testosterone may be used in some clinical situations (e.g. testosterone-deficient men), it (or synthetic versions) is used mainly by body builders to increase muscle growth and by athletes to increase muscle growth and performance. Testosterone, like other steroids, has multiple effects in the body. It not only promotes muscle growth, it is also an **androgen.** It causes the development of male sexual characteristics such as growth of chest and facial hair, growth of the testes and deepening of the voice (Figure 2). Other effects of testosterone include acne, fluid retention, increased libido, aggression and other psychological disturbances.

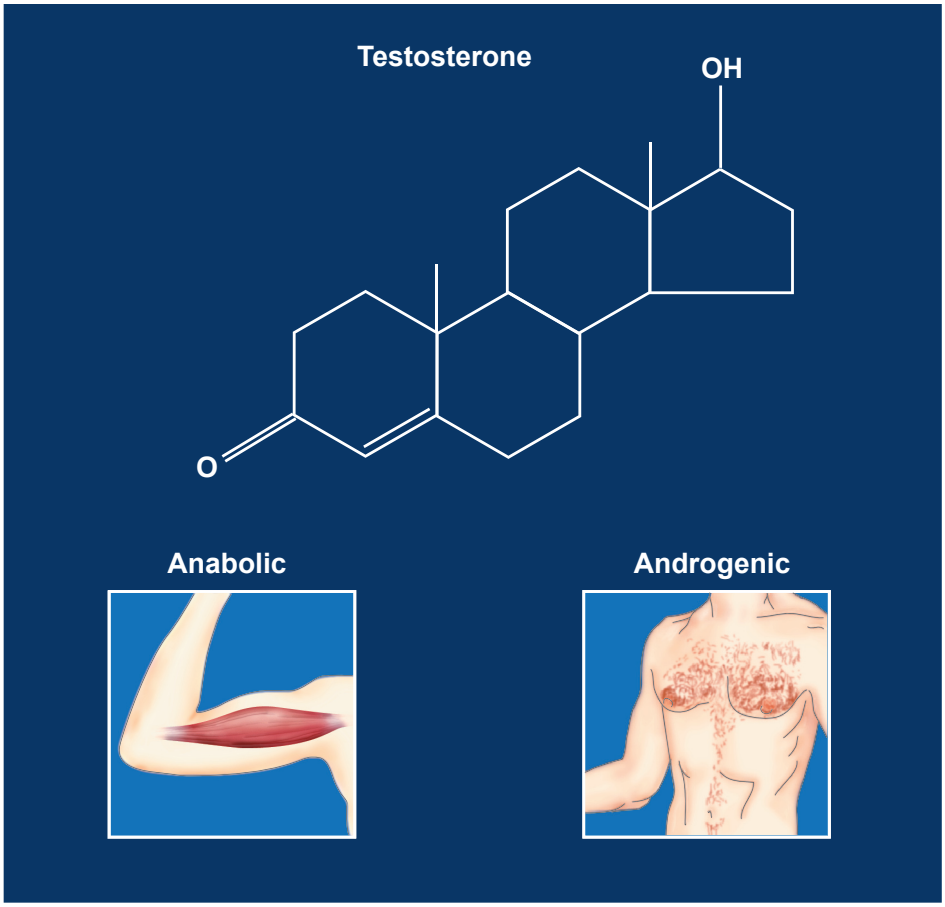


Figure 2. The structure of testosterone is shown. This steroid, synthesized in the testes, has both anabolic and androgenic properties.

Synthetic anabolic steroids

There are several problems with the use of testosterone. Since it has both androgenic effects (development of male sexual characteristics) and anabolic effects (promotion of muscle growth), both males and females may appear to be more "masculine." Athletes have tried to get around this issue by using synthetic forms of testosterone that have a chemical structure modified slightly from the original testosterone. These synthetic versions are called **anabolic steroids** and the manufacturers claim that they are more selective in their ability to produce anabolic effects compared to androgenic effects. However, despite these claims, anabolic steroids do have androgenic (masculinizing) effects, and thus a new terminology has emerged—anabolic-androgenic steroids, or AAS. The androgenic effects of anabolic steroids are a big problem for females who can develop facial hair, male pattern baldness and deepening of the voice (some of these effects are irreversible!). Another problem with taking the natural form of testosterone is that it is not very effective when given orally. After oral administration, testosterone is absorbed from the intestine into the bloodstream, which takes it to the liver (see Module 1), where it is immediately metabolized (inactivated). Thus, relatively little testosterone circulates throughout the bloodstream to reach its target. To address this problem, the chemists have chemically modified the testosterone structure to make it more difficult for the liver to metabolize it. The major chemical modification is the addition of C and H atoms (alkyl group) on the 5-membered ring at carbon #17 (**Figure 2**). Thus, this modification allows more testosterone to be available in the general circulation. However, there is a problem. The addition of an alkyl group at the 17th C atom not only enables the testosterone to be more slowly metabolized by the liver, but it also causes the liver to work harder to get rid of it, eventually resulting in liver damage or cancer.

How does an anabolic steroid reach its target?

Once in the bloodstream, the anabolic steroid travels to all tissues in the body, where it enters the cells to reach its target. In order to get into a muscle cell for example, the steroid must leave the capillary and then enter the muscle cell. This means that the steroid must cross two different types of membranes, the capillary membrane and the muscle cell membrane. To cross the capillary membrane, there are numerous pores or **fenestrae**, which allow small molecules to squeeze through (**Figure 3** and see Module 1). However the muscle cell membrane (like most cells in the body) does not have these small pores and therefore the steroid can only cross the membrane by diffusing across or by transport via a carrier protein. Steroids cross the muscle cell membrane by **passive diffusion**, which occurs in the direction of the concentration gradient— this does not require energy. Passive diffusion depends on the physiochemical characteristics of the membrane and the drug. The cell membrane, like all cell membranes in the body, is a lipid bilayer (**Figure 4**). It consists of lipids arranged with their polar head

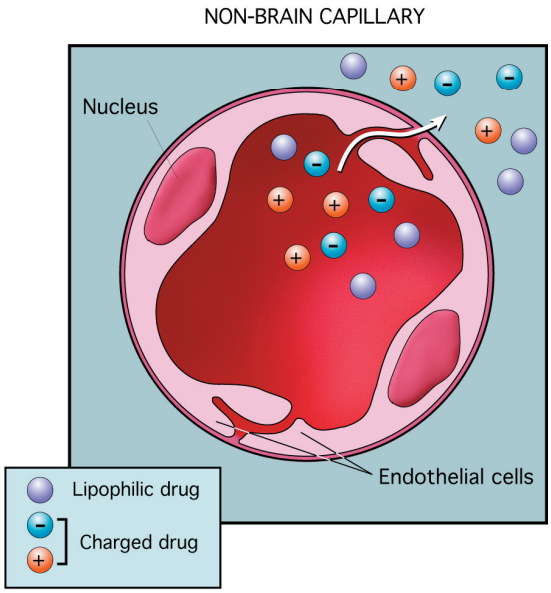


Figure 3. A capillary is composed of endothelial cells that connect together loosely. Small pores or *fenestrae* are also present, allowing solutes to move in and out of the capillaries.

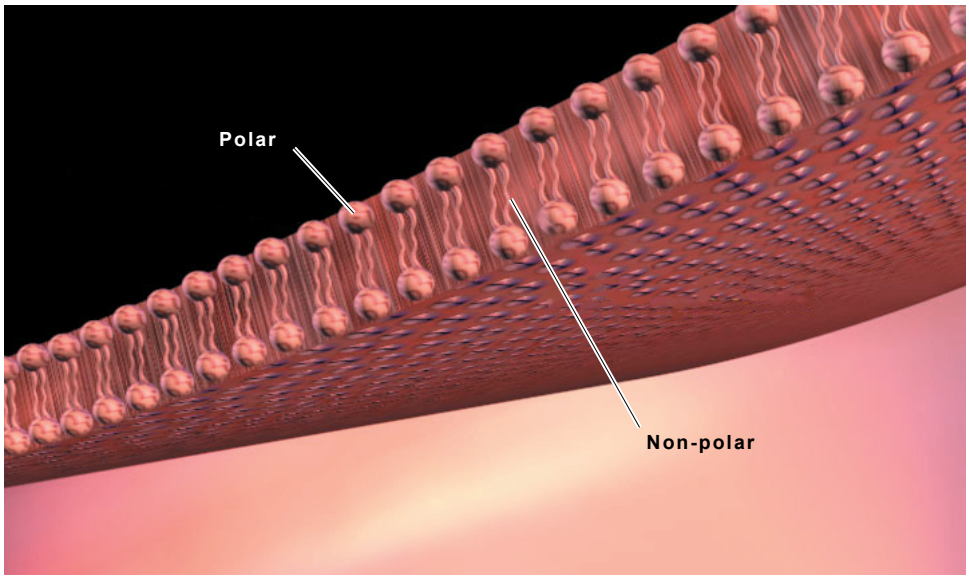


Figure 4. Schematic view of a cell membrane. Lipids are arranged with polar head-groups facing the outside and inside of the cell, while the fatty acid chains form the non-polar (hydrophobic) membrane interior.

groups facing the outside and inside of the cell. The chains of fatty acids face each other, forming the **hydrophobic** (water-fearing) or non-polar interior. Because anabolic steroids are very **lipophilic** (lipid-loving), they diffuse easily into the hydrophobic membrane interior. As they concentrate within the hydrophobic membrane interior, a new driving force is generated, pushing the steroid into the cytoplasmic side of the cell membrane. Once the anabolic steroid diffuses into the cytoplasm of the cell**,** it binds to the androgen receptor (**Figure 5**). [Receptors for other steroids are found in the nucleus instead of the cytoplasm.] This complex of steroid and protein then crosses the nuclear membrane to enter the nucleus of the cell, where it exerts its effects. In this case, passive diffusion can't occur because the protein is too large and not lipophilic. Instead, the steroid-receptor complex moves through small pores in the nuclear membrane to enter the nucleus. Although scientists are still elucidating exactly how this occurs, it is possible that the complex interacts with transport proteins that line the nuclear pores. This is an example of **facilitated diffusion,** which occurs in the direction of the concentration gradient. Therefore, no energy is required. This is unlike **active transport**, which occurs against the concentration gradient, and requires energy.

Steroids alter genetic function

Once inside the nucleus, the steroid-receptor complex binds to specific areas within the DNA (regulatory sites) to induce **gene transcription**, which directs the synthesis of specific proteins (**Figure 5**). A brief review of protein synthesis follows so we can understand how this happens.

DNA (deoxyribonucleic acid) is a large molecule containing the genes that code instructions for the synthesis of proteins. The code consists of a sequence of repeating subunits, or **nucleotides**. Each nucleotide has three parts: 1) a phosphate group (an acid), 2) a sugar (in the case of DNA, deoxyribose), and 3) a ring of carbon and nitrogen atoms (the nitrogen can form a bond with hydrogen so the nucleotide is basic) (**Figure 6**). A chain of nucleotides (**nucleic acids**) is formed by linking the phosphate group of one nucleotide to the sugar of an adjacent nucleotide. The bases stick out from the side of the phosphate-sugar backbone. The 3rd component described above, the base consisting of a ring of carbon and nitrogen atoms, occurs in 4 forms for DNA. These bases can be divided into two classes: the **purine bases** (adenine and guanine), which have double rings of nitrogen and carbon atoms, and the **pyrimidine bases** (cytosine and thymine), which have only a single ring. A molecule of DNA consists of two polynucleotide chains coiled around each other in the form of a double helix (**Figure 6**). The chains are held together by hydrogen bonds (see Module 5) between purine and pyrimidine bases – specifically, adenine is paired with thymine and guanine is paired with cytosine. Thus, one chain in the double helix is complementary to the other.

DNA is "read" by using three-base sequences to form "words" that direct the production of specific amino acids. These three-base sequences, known as triplets, are arranged in a linear sequence along the DNA. Each triplet codes for the synthesis of an amino acid and the specific chain of amino acids builds a specific protein. Most of the DNA is contained in the nucleus of the cell (a small amount is in the mitochondria), yet most protein synthesis occurs in the cytoplasm of the cell. Since DNA molecules are too large to pass through the nuclear membrane into the cytoplasm, a message must carry the genetic information from the nucleus into the cytoplasm. This message is carried by **messenger RNA** (mRNA; ribonucleic acid) molecules (Figure 5). The passage of information from DNA to mRNA in the nucleus is called **transcription** because the DNA sequence is actually transcribed into a corresponding RNA sequence. Once the mRNA passes through the nuclear membrane into the cytoplasm, it directs the assembly of a specific sequence of amino acids to form a protein – this process is **translation** (Figure 5). This occurs on ribosomes or in the rough endoplasmic reticulum (not shown in the figure). Thus, the synthesis of a protein is governed by the information in the DNA – mRNA simply serves as the messenger (and thus its name)! In the case of anabolic steroids, the steroid-receptor complex induces genes

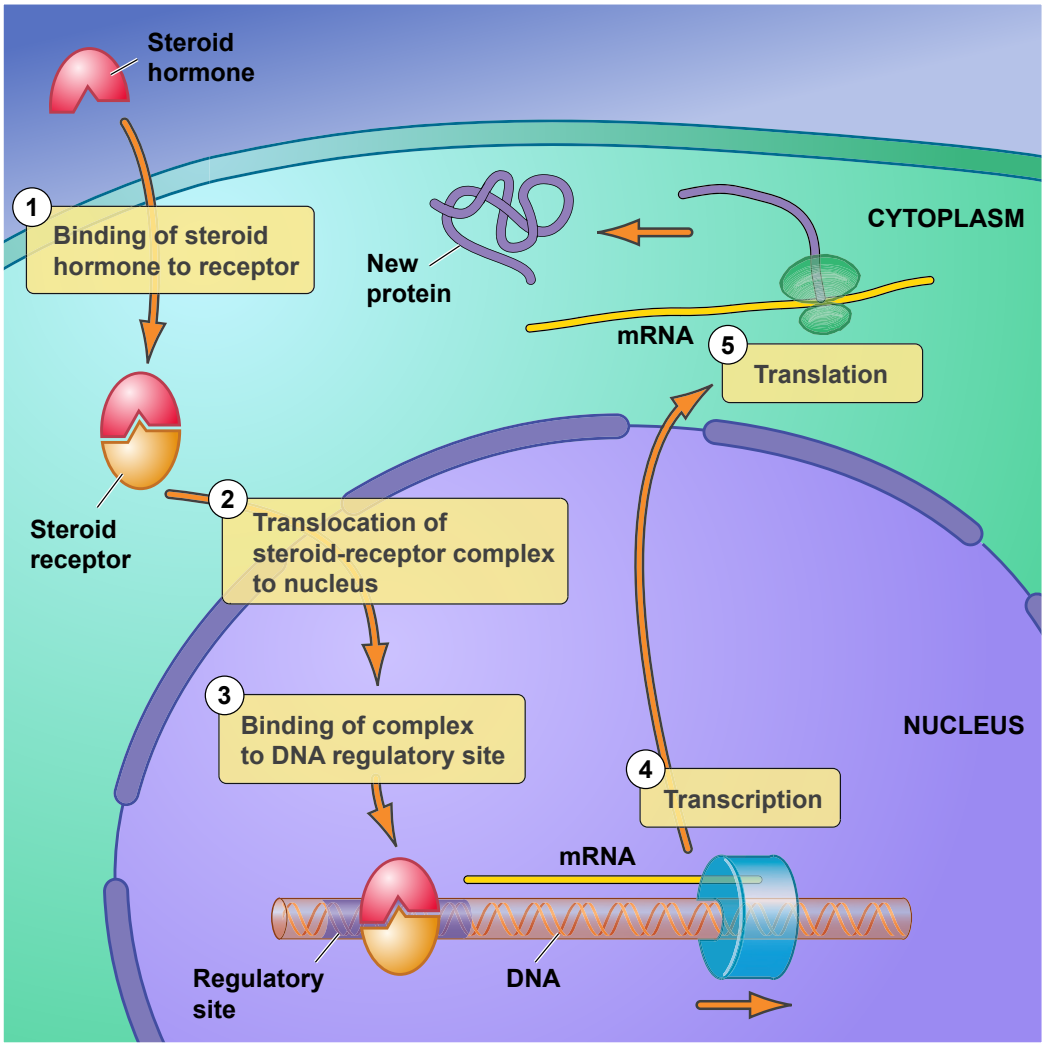


Figure 5. Testosterone (or anabolic-androgenic steroids) binds to the androgen receptor in the cytoplasm and the complex moves into the nucleus where it interacts with DNA to initiate protein synthesis.

to make specific proteins within muscle cells that help them to become larger and more powerful (discussed below). However, increased muscle growth is not the only action of anabolic steroids. Like testosterone, anabolic steroids can stimulate chest hair growth and cause acne and emotional problems (i.e., depression and hostility). The ability of anabolic steroids to produce these side effects is due to the cell type in which the steroid receptors are found and the specific DNA sequence that is transcribed. Thus, androgen receptors must be plentiful in cells of chest hair follicles (see Module 2), in secretory cells of sebaceous glands, and on neurons within the limbic system (important in mood) of the brain.

How does the alteration of genetic function by anabolic steroids increase muscle mass?

Consider the swimmer or weight-lifter who might use anabolic steroids (in fact both swimmers and weight-lifters in the 2000 Olympics were disqualified for steroid use). They have larger, more powerful arm muscles due to an increased production of specific proteins contained within skeletal muscle. A review of muscle structure will help us understand how this happens.

There are three main types of muscle in the body – skeletal, smooth, and cardiovascular. Steroids work predominantly on skeletal muscles, which account for approximately 40% of the 630 muscles in the human body!! Skeletal muscle cells contain a contractile mechanism that is activated by an electrical impulse generated when the neurotransmitter, acetylcholine, binds to acetylcholine receptors on the

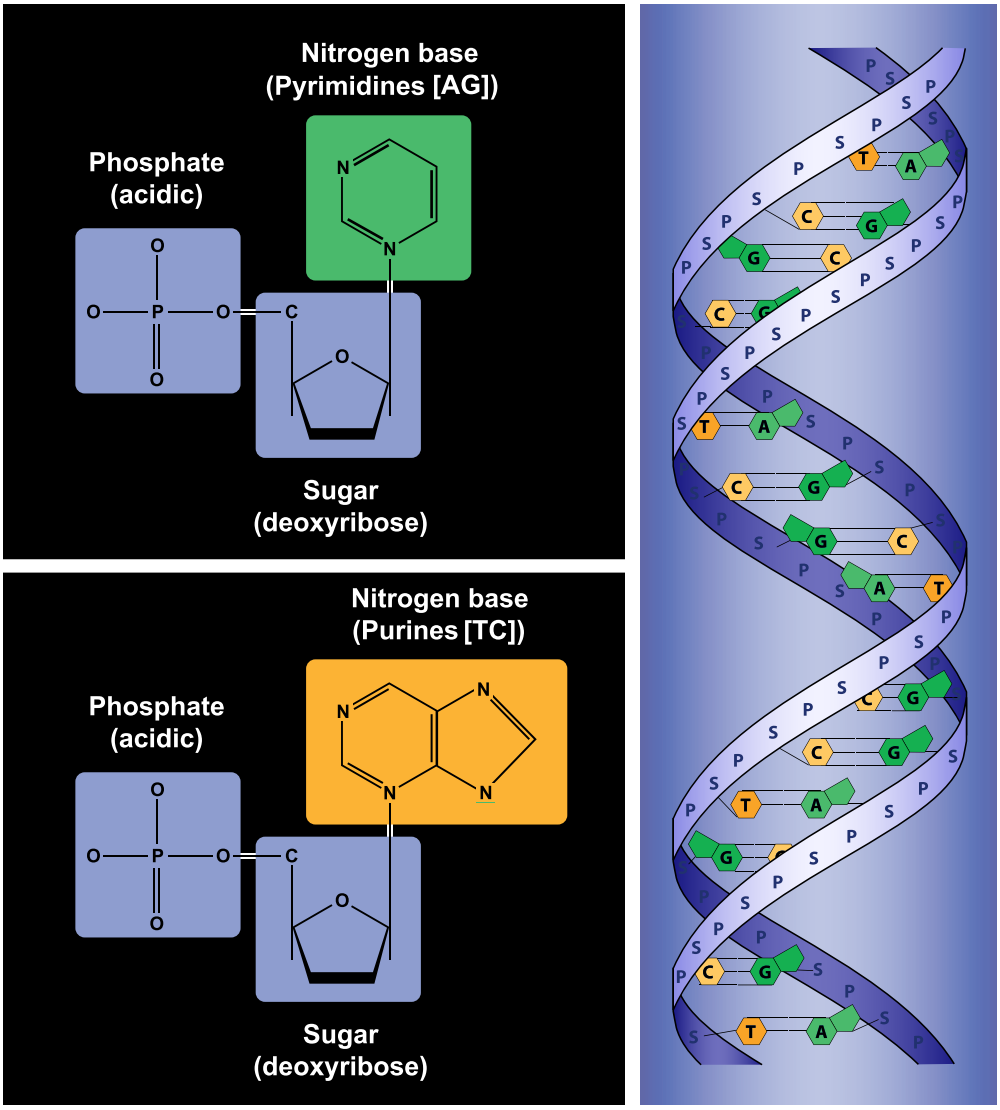


Figure 6. The generic structure of a nucleotide is shown. Nucleotides are joined together in a chain (phosphate groups of one nucleotide are linked with the sugar moiety of an adjacent nucleotide). The bases in one chain bind to complementary bases in another chain to form the double helical structure of DNA.

muscle (see Module 4). A single skeletal muscle cell is known as a muscle fiber (**Figure 7**). The term muscle refers to a number of muscle fibers bound together by connective tissue known as tendons, which are located at each end of the muscle. Skeletal muscle fibers (cells) appear striated because of an organized arrangement of thick and thin protein filaments (**myofibrils**) within cylindrical bundles in the cytoplasm--these myofibrils fill up most of the cytoplasm and extend from one end of a fiber to the other end. Each myofibril contains a repeating pattern of the thick and thin filaments surrounded by the sarcoplasmic reticulum and the sarcoplasm (cytoplasm). One unit of this repeating pattern is called a **sarcomere** (**Figure 8**). The thick filaments are composed of the contractile protein **myosin** and the thin filaments are composed of the contractile protein **actin**. Contraction occurs when the sarcomeres shorten by the action of the myosin filaments sliding over the actin filaments. The sliding of the myosin filaments is initiated when acetylcholine binds to its receptor in the muscle cell, generating an electrical signal to release calcium from the sarcoplasmic reticulum (where it is sequestered) into the sarcoplasm. The muscle relaxes when the calcium is removed from the sarcoplasm back into the sarcoplasmic reticulum by the enzyme calcium-ATPase.

For advanced students:

The cellular mechanism for muscle contraction
Actin contains active sites to which myosin binds during contraction. When the muscle is relaxed, the active sites are covered by another protein called tropomyosin, preventing any contraction. Troponin molecules are located along the actin-tropomyosin filaments and they help position the tropomyosin filaments over the active sites on the actin filaments. When calcium enters the sarcoplasm, troponin undergoes a conformational change that results in the movement of tropomyosin off the active sites, allowing myosin and actin to interact. The uncovering of the active sites allows myosin heads to bind to the actin active sites, initiating a movement of the myosin head toward the center of the sacromere. This pulls the actin along and shortens the sarcomere, thus causing the contraction. Each of the myosin heads operates independently of the others, each attaching and pulling in a continuous alternating ratchet cycle. This cycle stops when the calcium is removed from the sarcoplasm (as described above), causing troponin to change its conformation back to the resting state. The tropomyosin can then "cover up" (rebind to) the active sites causing the muscle to relax.

Anabolic steroids will induce the genetic machinery (as discussed above) in muscle cells to synthesize more muscle proteins. More contractile proteins make the muscle cell bigger, and therefore, the whole muscle gets bigger. Muscle growth is aided by another important action of anabolic steroids. Anabolic steroids can also bind to glucocorticoid receptors (there is some similarity in the structure of androgen and glucocorticoid receptors), preventing glucocorticoids from carrying out their normal **catabolic** or muscle-breakdown activity. Athletic performance improves as the muscles grow. The performance-enhancing effects of anabolic steroids do not occur in people who are not exercising unless large doses are used. Athletes tend to believe that the more steroids they take, the bigger their muscles will become. However, this doesn't happen. There are only a finite number of steroid receptors in the muscle cell. Thus, when all of the receptors are bound to the steroid (i.e., the receptors become saturated), any additional steroid molecules remain in the bloodstream, where they travel to the liver and kidneys. The high levels of steroids presented to the liver and kidneys can cause damage. High doses of anabolic steroids can have other adverse effects too. They can actually increase protein breakdown during the muscular stress that occurs with intense athletic training, increase fluid and electrolyte retention, or produce an increase in body weight.

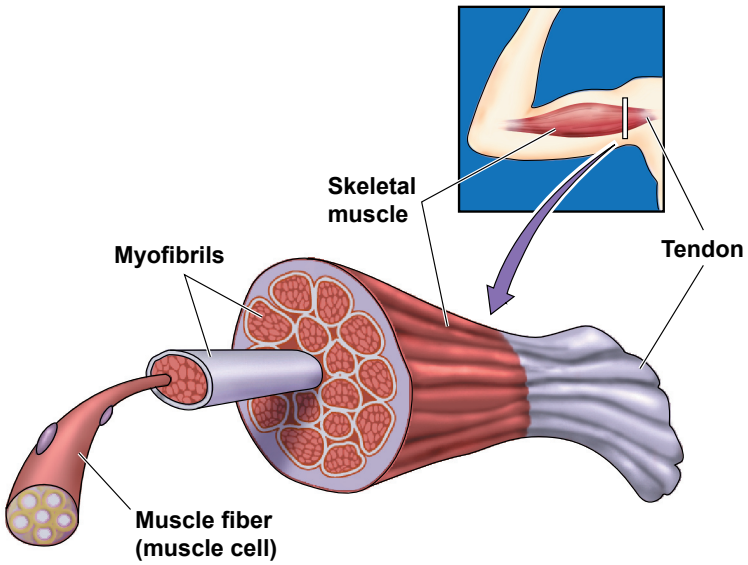


Figure 7. A skeletal muscle cell (also called a muscle fiber) is shown containing several myofibrils. These protein filaments are important in muscle contraction.

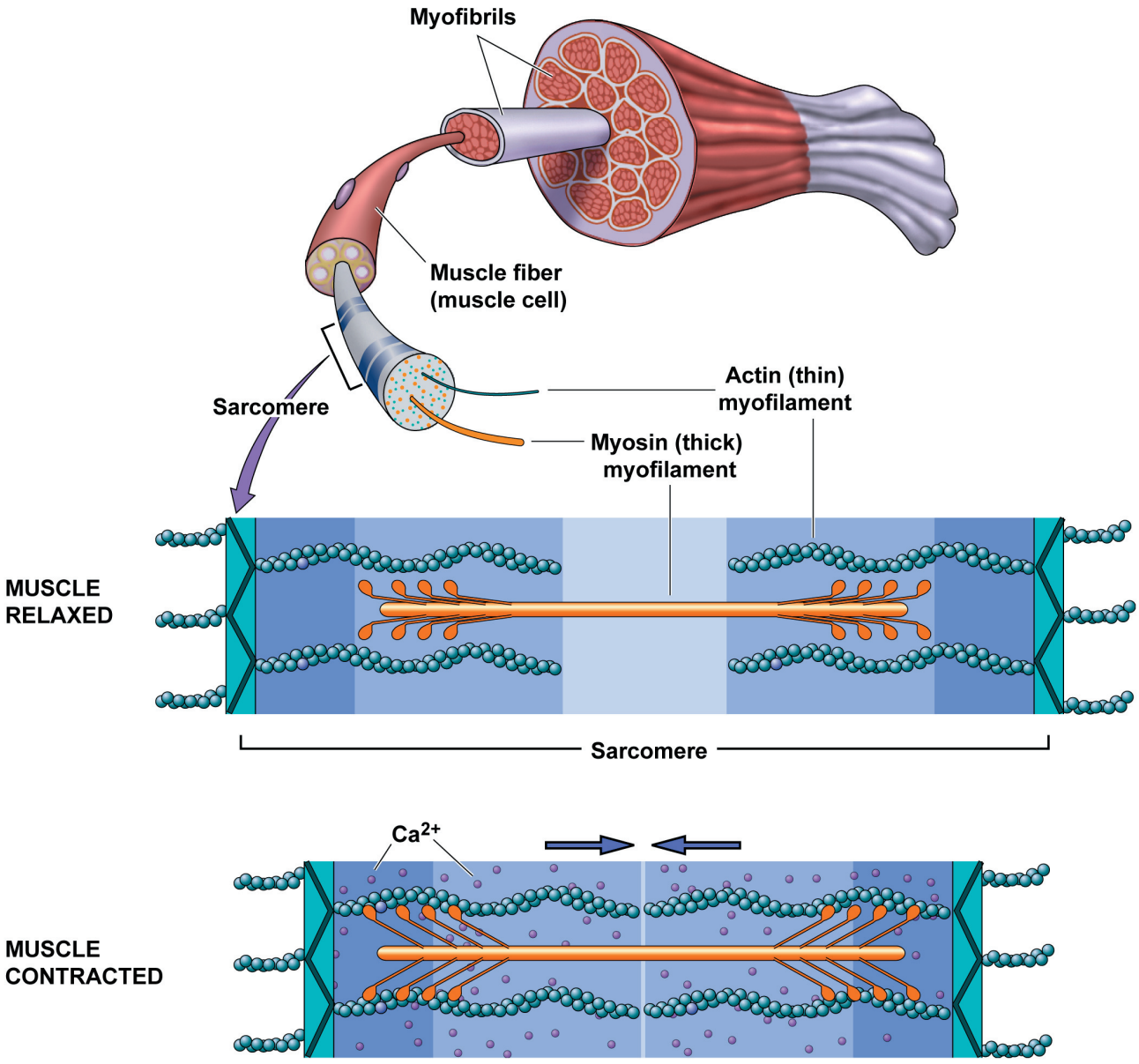


Figure 8. The repeating pattern of thick and thin filaments is a sarcomere. The presence of calcium causes sarcomeres to shorten when actin filaments slide over the myosin filaments. This produces muscle contraction. (After Seeley, et. al. Essentials of Anatomy and Physiology. Boston, MA: Mc-Graw-Hill, 1999.)

Why can anabolic steroids be detected in the body for long periods of time?

Every athlete knows that his/her urine will be tested for drug use when they enter an important competition. To avoid detection of steroids in their urine, athletes will stop using the drugs well before the competition. Yet, in many cases, steroids can still be detected long after the athlete stops using them (even weeks later!). The reason for this lies in the chemical structure of the anabolic steroid. As discussed above, anabolic steroids are very lipophilic molecules. This property makes it very difficult for the drug to remain long enough in the liver to be metabolized (inactivated) or in the kidney to be excreted in the urine (**Figure 9**). The lipophilic drug moves with its concentration gradient from the liver or the kidney cells right back into the bloodstream. Thus, it doesn't get eliminated very well. Instead,

it seeks out fat cells that exist in the athlete (these are much smaller than those found in the average couch potato!). The lipophilic steroid likes to enter fat cells, and with repeated use, the steroid accumulates there. When the user stops taking the steroid, the blood levels decline rather quickly in the absence of the drug. But now, the steroid concentration inside the fat cell becomes greater than that in the blood, so the concentration gradient reverses in the direction of fat cell-to-blood capillary. The fat cells are like a storage depot, releasing small amounts of steroid into the blood over time (via passive diffusion). Eventually the steroid gets metabolized and makes its way to the kidney to be excreted in the urine. This explains why it is possible to detect small amounts of the steroid in the urine at competition weeks after the athlete stops using it.

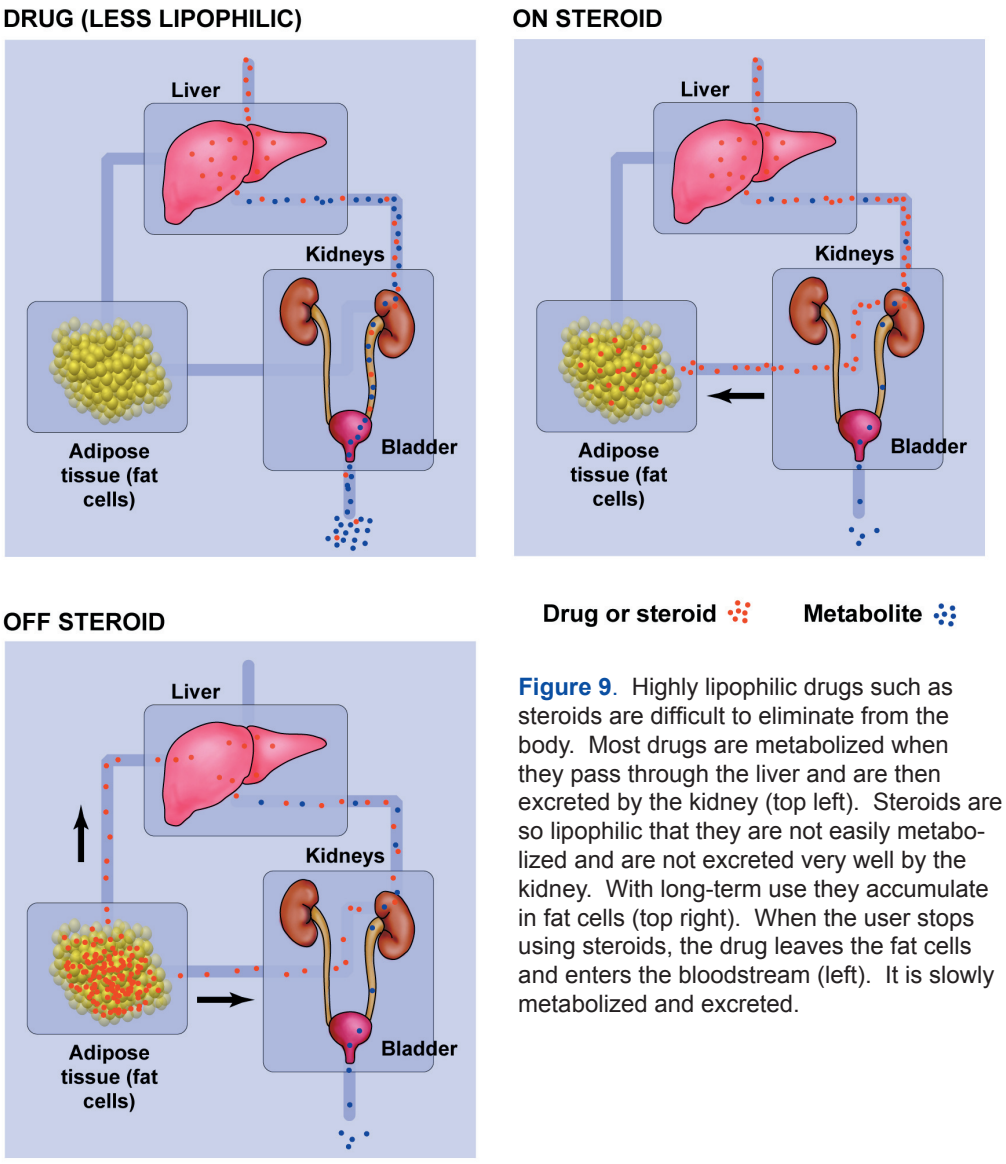


Figure 9. Highly lipophilic drugs such as steroids are difficult to eliminate from the body. Most drugs are metabolized when they pass through the liver and are then excreted by the kidney (top left). Steroids are so lipophilic that they are not easily metabolized and are not excreted very well by the kidney. With long-term use they accumulate in fat cells (top right). When the user stops using steroids, the drug leaves the fat cells and enters the bloodstream (left). It is slowly metabolized and excreted.

Why can't users stop taking steroids abruptly? Is it an addiction?

The answer is "not really." An **addiction** to a substance indicates that the person uses the drug compulsively, with a loss of control in their intake, despite negative consequences. Most athletes are not compulsive users of steroids (although there may be a few out there!)—if they were, they would not be able to stop taking the steroids prior to competition. However, chronic users can become dependent on steroids. A **dependence** means that the athlete's body adapts to the presence of the steroid, and if the steroid is withdrawn suddenly, physiologic symptoms emerge. Withdrawal symptoms include

nausea, headaches, dizziness, increased blood pressure, decreased libido (sex drive), depression and craving. The basis for this dependence involves the brain and the gonads. More specifically, the hypothalamus, found at the base of the brain, releases hormones that direct other tissues in the body to produce steroids (**Figure 10**). In the case of the sex steroids, the hypothalamus produces a hormone called "gonadotropin releasing factor" or GNRH. This hormone binds to GNRH receptors on the pituitary gland (located near the hypothalamus, but not actually part of the brain), where it activates the release of lutenizing hormone (LH) and follicular stimulating hormone (FSH). These pituitary hormones travel throughout the bloodstream and when they reach the gonads (i.e., testes and ovaries), they bind to LH and FSH receptors in gonadal cells to cause the release of testosterone and estrogen. The body attempts to keep the steroid levels in balance using "feedback regulation." When the sex steroid levels in the blood become elevated, the hypothalamus reduces its production of GNRH, the pituitary reduces production of LH and FSH, and the gonads reduce production of testosterone and estrogen. [In women taking birth control pills, this is the basis for the contraceptive activity—without enough LH and FSH, they can't ovulate.] So, when the athlete takes the steroids chronically, his/her hypothalamus stops producing GNRH and the gonadal tissues stop producing testosterone or estrogen due to this negative feedback. Now, if athletes stop taking the steroids abruptly, they won't have enough testosterone or estrogen. It takes some time (it can take 6 months!) for their hypothalamus, pituitary, and gonads to recover normal activity and start producing these hormones again. Therefore, all people who use steroids, even for therapeutic purposes, must taper off the drug slowly to give their hypothalamus, pituitary and gonads time to recover normal hormone production.

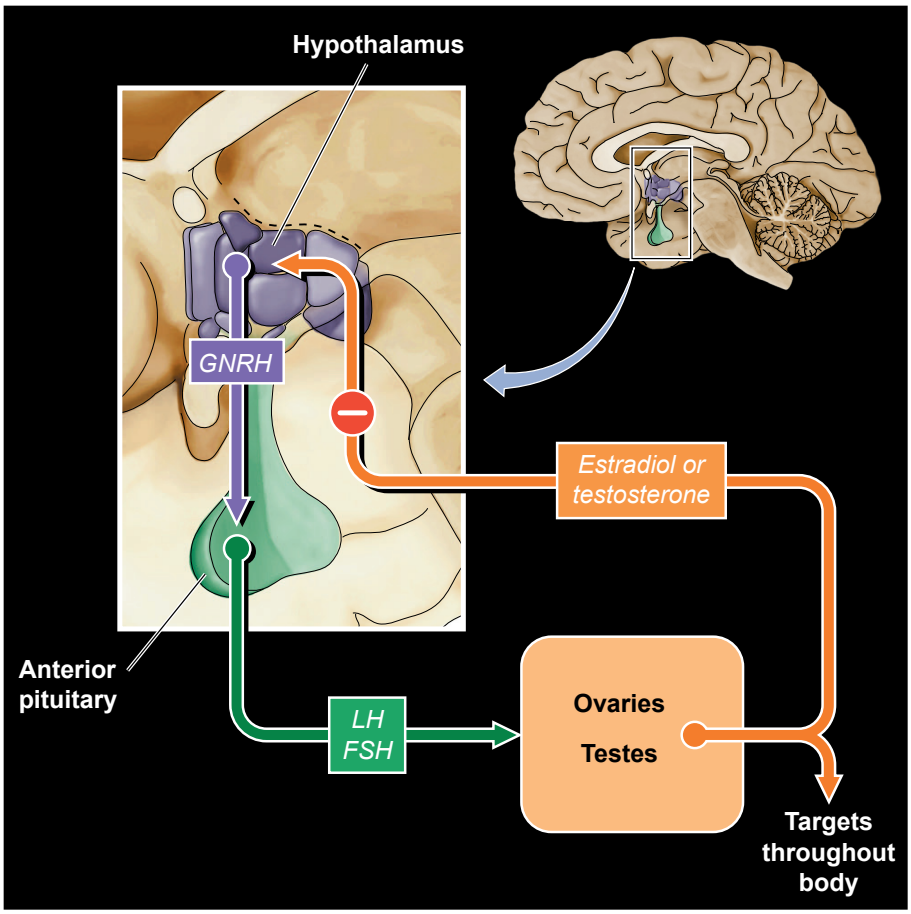


Figure 10. The hypothalamus-pituitary-gonadal "axis" is shown. GNRH is released by the hypothalamus, signaling the pituitary gland to release LH and FSH into the blood. In males, the testis synthesizes and releases testosterone in response to the LH and FSH. Circulating testosterone signals the hypothalamus to shut down GNRH release ("feedback inhibition").

Glossary

actin – contractile protein that is present in the thin filaments of the myofibrils.

active transport – the movement of molecules against the concentration gradient with the help of a transport protein. This transport requires energy in the form of ATP.

addiction – a behavior pattern that occurs when a person uses drugs compulsively, with a loss of control of their intake, despite negative consequences.

anabolic steroids – synthetic versions of testosterone designed to promote muscle growth without producing androgenic effects. The better term is anabolic-androgenic steroid.

androgen – a steroid hormone such as testosterone that is masculinizing (deepens voice, produces facial & chest hair, sperm production)

catabolic – a compound that causes the breakdown of muscle resulting in the net loss of nitrogen from the body. Glucocorticoids are catabolic in skeletal muscle.

dependence – the body functions normally in the presence of the drug. When the drug is present, the body has adapted physiologically to its presence. When the drug is removed, withdrawal symptoms are produced, usually in opposition to the effects produced by the drug's presence.

DNA (deoxyribonucleic acid) – a large molecule containing the genes that provide the instructional code for the synthesis of proteins. DNA consists of two complementary polynucleotide chains coiled around each other in the form of a double helix.

facilitated diffusion – the movement of molecules across a membrane with the concentration gradient. No energy is required, but transport proteins can become saturated, limiting the diffusion process.

fenestrae – small spaces or pores between endothelial cells that form the capillary membrane. These pores allow charged drugs or larger drugs to pass through the capillaries.

hormones – chemicals in the body that are synthesized in one tissue and secreted into the bloodstream for actions in tissues some distance away. They regulate many physiologic functions.

hydrophobic – "water-fearing"; a compound that is soluble in fat but not water. This is typical of compounds with chains of C atoms.

lipophilic – high lipid solubility. Lipophilic compounds dissolve readily in oil or organic solvent. They exist in an uncharged or non-polar form and cross biological membranes very easily.

messenger RNA – also known as mRNA or ribonucleic acid; it is transcribed from DNA and moves to the cytoplasm to direct protein synthesis.

myofibrils – a repeating pattern of thick (myosin) and thin (actin) protein filaments that are organized in cylindrical bundles within the sarcoplasm. The myofibrils extend from one end of a muscle fiber to the other end.

myosin – contractile protein that is present in the thick filaments of the myofibrils.

non-polar - a chemical property of a substance that indicates an even distribution of charge within the molecule. A non-polar or non-charged compound mixes well with organic solvents and lipids but not with water.

nucleic acid – a chain of repeating subunits of nucleotides.

nucleotides – the hydrolysis product of nucleic acids comprising 3 parts: 1) a phosphate group (an acid), 2) a sugar (deoxyribose for DNA and ribose for RNA), and 3) a ring of carbon and nitrogen atoms (nucleosides; purines and pyrimidines).

passive diffusion – the net movement of molecules from higher to lower concentrations. This form of diffusion does not require an energy source to occur.

polar compound – a chemical property of a substance that indicates an uneven distribution of charge within the molecule. A polar substance or drug mixes well with water but not with organic solvents and lipids. Polar or charged compounds do not cross cell membranes (lipid) very easily.

purine base – a type of nucleotide present in DNA that consists of double rings of carbon and nitrogen atoms. The two purine bases present in DNA are adenine and guanine.

pyrimidine base – a type of nucleotide present in DNA that consists of a single ring of carbon and nitrogen atoms. The two pyrimidine bases present in DNA are cytosine and thymine.

ribosomes – structures within the cytoplasm consisting of proteins and a different form of RNA (rRNA) that support the process of protein translation

sarcomere – one unit of a repeating pattern of actin and myosin present in a myofibril.

steroids – a class of hormones synthesized from cholesterol by specific cells in the body. They are powerful compounds that alter genetic function, causing numerous effects in the body.

transcription – the passage of information from DNA to mRNA in the nucleus; this is directed by several enzymes.

translation – the process of assembling a specific sequence of amino acids (based on the instructional code provided by mRNA) to form a protein. It occurs in the cytoplasm on ribosomes or in the rough endoplasmic reticulum.

Resources

The following resources provide supplemental information that pertains to the topic in this module.

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CE Yesalis and MS Bahrke. Anabolic-Androgenic Steroids: Current Issues. Sports Medicine, 19: 326-340, 1995. or http://www.naturalstrength.com/steroids/detail.asp?ArticleID=382

JM Hoberman and CE Yesalis. The history of synthetic testosterone. Scientific American. 272: 76-81, 1995.