Individual susceptibility to toxicity

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SUMMARY

Individual variation in susceptibility to chemical toxicity may be due to differences in toxicokinetic patterns or effect modification. Well-documented interspecies genetic differences in susceptibility to chemicals had lead to studies of such variation also within species. Epidemiological evidence now suggests that common variations, particularly in the P-450 enzymes, may play a major role in determining individual susceptibility to chemically-induced disease. Physiologic factors are involved in the particular susceptibility of the fetus, the newborn, and the old. Constitutional susceptibility is also affected by acquired conditions, including chronic disease, such as diabetes mellitus. Perhaps the most complex area relates to the increase in vulnerability caused by previous or contemporary exposure to other factors, thus eliciting, e.g., synergistic effects. Although amply demonstrated by experimental studies, epidemiological or clinical confirmation is generally lacking. One hypothesis suggests that a chemical exposure may affect the reserve capacity of the body, though not resulting in any immediate adverse effect. Subsequently, the body becomes unable to compensate for an additional stress, and toxicity then develops. Epidemiological approaches are available and need to be expanded. Research in this area has potential ethical implications which should be dealt with in an open, informed forum.

SIGNIFICANCE OF INDIVIDUAL VARIATION

From a positivistic viewpoint, biological phenomena observed in toxicological studies may be looked upon as systematic processes obscured by variance. To limit the influence of this variance and uncover underlying processes, relatively uniform groups are often studied. However, by emphasizing the differences between well-defined averages, we tend to neglect the importance of individual variation. Some of the variance may be caused by the existence of subpopulations with different degrees of sensitivity or

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ability to respond. While several types of variation can be defined [1], this paper will be restricted to those that can be regarded systematic and related to specific causes.

Individual susceptibility within a species may be defined as the reciprocal of the dose needed to produce a standardized response [2]. Hypersusceptible individuals will experience an adverse health effect to one or more chemicals at significantly lower or shorter exposures than the general population. An important research purpose is therefore to characterize the factors that predispose individuals to toxic effects.

Both toxicokinetic and toxicodynamic mechanisms may affect individual predisposition to toxic effects. The mechanisms may be classified into three types: (1) Factors that increase the concentration of the biologically active substance at the active site; (2) Factors that augment the reaction of the chemical substance with target molecules in the body, thereby initiating the response; and (3) Factors that promote the sequence of events between the initial reaction and the final manifestation of an adverse health effect [3].

Knowledge about individual susceptibility may be important to reduce the risk of disease in employees or consumers. Early diagnosis would potentially give hypersusceptible individuals an opportunity to plan their life to reduce the impact of their vulnerability. Failing to detect and warn such individuals at risk could be culpable. The fortunate ones not found to be hypersusceptible will also benefit from this information. However, ethical conflicts may occur and must be addressed.

VALIDITY OF THE DATA BASE

The extent of intraspecies variation can be determined from different types of data. The steepness of the dose–response curve in LD$_{50}$ experiments [4] has suggested that a safety factor of 10 may, in 92% of the cases, be sufficient to include members of the population within three standard deviations [5]. However, this information is based on acute toxicity in particular rodent strains only. Limited pharmacokinetic studies of 101 chemicals, mainly drugs, only identified one instance of wide variation in a small number of healthy adults [2]. However, variant enzymes occur quite commonly, and even slight decreases of activity could affect the degree of susceptibility [6]. Variations in enzyme activity may exceed 100-fold [7], and this mechanistic information would suggest that a safety factor of 10 may not be sufficient to protect hypersusceptible individuals. Epidemiological research has thrown additional light on this hypothesis, but most studies relate to drug metabolism or risk factors for cancer.

Epidemiological studies of hypersusceptibility to toxic effects face several difficult problems. Exposures to chemicals other than prescribed drugs are
often poorly characterized. In addition, signs and symptoms caused by chemical exposure are to a large extent nonspecific [8]. However, the fact that many adverse health outcomes have a multifactorial causality is a main reason that variations in susceptibility occur.

Current evidence on the types of causes involved will be outlined below, and epidemiological examples will be given, in particular for lead. For didactic reasons, the factors are separated into three groups, i.e. genetic, constitutional, and environmental, although some overlapping between these groups will be apparent.

CAUSES OF HYPERSUSCEPTIBILITY

Genetic

The term ecogenetics refers to variations on a hereditary basis in the response to xenobiotics. Research in this area has been stimulated by the discovery of genetic polymorphisms for numerous enzymes that metabolize foreign compounds and by recent technological advances [7]. The health significance is in many cases unclear, and the metabolic defects may be covert, only to be revealed if challenged by one or more chemicals that precipitate the idiosyncratic response.

In epidemiological studies, ecogenetic biomarkers have shown significant relations with certain types of malignancy [9]. For example, the cytosolic N-acetyltransferases exhibit ecogenetic differences, and “slow” acetylators have an increased risk of both bladder cancer and isoniazid-induced neurotoxicity [10]. Similar relations have been demonstrated with some cytochrome P450 enzymes. Thus, individuals with “extensive” debrisoquine 4-hydroxylase (CYP2D6) activity appear to run an increased risk of developing cancer [11]. While these enzymes are potentially involved in activation or detoxication, heterogeneities may also exist with regard to repair of the damages induced, e.g., the activity of O6-methylguanine-DNA-methyltransferase [12]. Even with inorganic substances, such as lead, hereditary factors may also play a role [13].

Although epidemiological associations may appear quite convincing, the biological mechanisms involved are still open for interpretation, and the possibility of linkage with other important genes has yet to be explored in detail. However, the evidence tends to support the notion that inherited factors are involved to a considerable extent in determining individual susceptibility to toxic effects of environmental chemicals.

Constitutional

Sex and age are major constitutional determinants of responses to chemical exposure. While women may be considered the weaker sex, men carry
Fig. 1. Hemoglobin-adjusted blood-lead concentrations (nmol/l) in 100 women. The thick regression line shows the age-related increase in blood-lead for all women, the thin line is for premenopausal women, and the dashed line is the regression line for men [14].

the main part of occupational exposure to chemicals. With regard to toxicokinetic factors, women have the benefit, e.g., of being able to transfer certain chemicals to the fetus and excrete the chemicals in breast milk, thus limiting their own chemical burdens while passing the risk on to the progeny. With regard to hormonal factors, a cross-sectional study of 200 randomly selected men and women of the general population [14], showed that the age-related increase in the blood-lead concentration was particularly steep in postmenopausal women (Fig. 1). This increase is probably caused by a release of lead from the skeleton due to postmenopausal osteoporosis [15], and the skeleton is also a much less efficient storage depot for lead in children.

In neonates and small children, the relative gastrointestinal absorption will be increased due to the greater permeability of the intestinal epithelium. An additional factor is the colonization of the gut with demethylating bacteria that affect the disposition of methylmercury, and this appears to happen only after weaning [16]. Excretion via the urine depends on the glomerular filtration, urine flow, pH, etc., as in the case of fluoride [17]. Old age is associated with alterations in xenobiotic disposition, as reflected in,
e.g., P450 enzyme activities, in part due to changes in enzyme induction [18]. Some lipophilic compounds may be retained to a greater extent in aged animals, partly because of their larger fat depots; less efficient detoxication and excretion may also play a role [18].

With regard to toxicodynamic variations, the immature organism is generally at particular risk, perhaps in particular with regard to neurotoxicity. In a study of lead neurotoxicity, none of the 160 children examined had a birth weight below 2500 g, but mild neonatal jaundice occurred in 44 of them [19]. A history of neonatal jaundice was a significant risk factor for poor neuropsychological test performance, but only in children with increased lead exposure. This tendency was particularly obvious with the Bender Gestalt test that was also the test most sensitive to lead neurotoxicity. Thus, despite the fact that the hyperbilirubinemia was below current action levels, the combination with high lead exposure seemed to unmask an individual susceptibility to neurotoxicity.

Environmental

An individual's resistance toward chemical toxicity may be affected by other environmental exposures, including those associated with diet and lifestyle. Most obvious interactions may be seen in individuals who suffer from a pre-existing (non-heritable) disease or who are exposed to other toxic hazards at the same time or who have been exposed in the past. For example, liver cirrhosis seems to increase the retention of lead by impeding the excretion [20].

The human body has a certain capacity to withstand potentially adverse effects of chemical exposures. Thus, an exposure may not necessarily result in immediate toxicity, but could conceivably cause a weakening of the body defenses, i.e., a decrease in reserve capacity. This effect may not be readily observable, but it could cause an increased susceptibility to subsequent exposures to other hazards.

To examine the possible significance of this factor, we examined the blood regeneration following phlebotomy in 25 men with legally acceptable occupational lead exposure as compared to a control group of 25 other industrial workers [21]. On day 15, the lead workers showed a significant delay in blood regeneration (Fig. 2). Thus, despite the normal hematological findings on the first examination, the lead exposure had apparently caused a decreased reserve capacity for blood formation, and this effect became evident only due to the unmasking effect of the phlebotomy.

Certain degenerative neurological diseases, such as parkinsonism and amyotrophic lateral sclerosis, may be due to accumulated effects of age and environmentally-induced damages [22]. Many years after an exposure to neurotoxins, normal cell attrition and, perhaps, cumulation of other adverse
Fig. 2. Median hemoglobin (mmol/l) and erythrocyte count (x 10^{12}/l) in 25 lead-exposed workmen and in 25 controls at the time of phlebotomy (0.45 l) and 15 days later when blood regeneration should have compensated for most of the blood loss (*p<0.01; **p < 0.05) [21].

influences may unmask the dysfunctions. Similarly, risks for mental handicaps depend upon sociodemographic conditions [19,23], and such non-neurotoxic factors may affect the reserve capacity for compensation as well. The kidneys also have a functional reserve capacity [24]. Nephrotoxic chemicals or kidney disease may affect this reserve capacity, thereby rendering the kidneys more susceptible to subsequent damage. Accordingly, patients with diabetes appear more susceptible to cadmium-related nephrotoxicity [25].

The existence of various degrees of reserve capacity in different organs will obviously modify the individual susceptibility in human populations. Thus, if chemical exposures have tapped the reserves even without causing frank disease, the individuals concerned could be particularly vulnerable when they meet their next exposure.

ETHICAL ISSUES

Research on individual susceptibility is often looked upon as ethically dubious. True, the results obtained are subject to potential misuse. However, no area of science is entirely free of such risk. Thus, a constructive course of action would be to examine in depth the ethical issues concerned,
to engage our colleagues in a consideration of ethical values in their research and to promote public discussion at a well informed level [26].

Moral obligations do not provide detailed guidance, and conflicts are likely to occur, e.g., with regard to the superiority of beneficence or respect for autonomy. Controversy may relate to the acceptability of paternalistic measures, such as, infringement on liberty because the person’s own choice could be harmful to himself or herself.

Testing for susceptibility may infringe upon individual freedom and rights to privacy. The result of a predictive screening test will inevitably be of interest to others besides the person at risk, and this fact may lead to ethical conflicts. A balance should be sought between the interests of the individual and those of society. Most emphasis has so far been placed upon the risks of susceptible individuals, but the rights of the resistant ones should not be disregarded.

RESEARCH NEEDS

Intraspecific variability needs further exploration in experimental studies. Mechanistic studies are needed to illuminate the processes involved in individual susceptibility. For instance, deficiencies may occur in the activity of epoxide hydrolase, an enzyme that detoxicates reactive intermediates, and the consequences of the well-established variation of glutathione transferases need to be explored [7]. Experimental studies are generally carried out under controlled circumstances, often with inbred strains, that limit the extent of individual variability in the response to chemical exposure [27]. To obtain more information on variability, outbred strains and strains with specific gene mutations should be used more extensively, and the designs should incorporate different ages and combinations of risks.

Similarly, epidemiological studies should focus on well-defined interaction parameters. Although the methodology for identifying effect modification and susceptibility is controversial [28], ideal conditions would entail prospective studies with well-documented exposures. Again, past research has maximized the study power by focusing on well defined and homogeneous populations, e.g., in studies of lead neurotoxicity in groups of children with low background risks [19,23]. Unfortunately, such restriction of the study population then limits the possibility of identifying interaction parameters that may relate to hypersusceptibility.

In both experimental and epidemiological studies, biomarkers of exposure, disease, and susceptibility offer considerable promise for future developments. If relevant polymorphic genetic markers are yet unknown, DNA could be isolated and stored for later analysis. In addition, heritable factors could be studied in twin populations. The notion of functional reserve
capacity is probably very useful for the understanding of some forms of non-heritable hypersusceptibility. As already documented, the absence of an adverse effect in association with a current or recent exposure may not be a guarantee that the exposure has been innocuous. The general validity of this hypothesis deserves to be explored.

In a pluralistic society, the ethical questions cannot be resolved by scientists alone or by any other group in isolation. The ethical conflicts should be outlined, and a resolution should be sought in an open, informed forum. Researchers therefore need to encourage and participate in a public discourse on these concerns.

REFERENCES


