Are we dependent upon coffee and caffeine?
A review on human and animal data

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Abstract

Caffeine is the most widely used psychoactive substance and has been considered occasionally as a drug of abuse. The present paper reviews available data on caffeine dependence, tolerance, reinforcement and withdrawal. After sudden caffeine cessation, withdrawal symptoms develop in a small portion of the population but are moderate and transient. Tolerance to caffeine-induced stimulation of locomotor activity has been shown in animals. In humans, tolerance to some subjective effects of caffeine seems to occur, but most of the time complete tolerance to many effects of caffeine on the central nervous system does not occur. In animals, caffeine can act as a reinforcer, but only in a more limited range of conditions than with classical drugs of dependence. In humans, the reinforcing stimuli functions of caffeine are limited to low or rather moderate doses while high doses are usually avoided. The classical drugs of abuse lead to quite specific increases in cerebral functional activity and dopamine release in the shell of the nucleus accumbens, the key structure for reward, motivation and addiction. However, caffeine doses that reflect the daily human consumption, do not induce a release of dopamine in the shell of the nucleus accumbens but lead to a release of dopamine in the prefrontal cortex, which is consistent with caffeine reinforcing properties. Moreover, caffeine increases glucose utilization in the shell of the nucleus accumbens only at rather high doses that stimulate most brain structures, non-specifically, and likely reflect the side effects linked to high caffeine ingestion. That dose is also 5–10-fold higher than the one necessary to stimulate the caudate nucleus, which mediates motor activity and the structures regulating the sleep-wake cycle, the two functions the most sensitive to caffeine. In conclusion, it appears that although caffeine fulfils some of the criteria for drug dependence and shares with amphetamines and cocaine a certain specificity of action on the cerebral dopaminergic system, the methylxanthine does not act on the dopaminergic structures related to reward, motivation and addiction. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Caffeine; Dependence; Withdrawal; Tolerance; Discrimination; Drugs of abuse

1. Introduction

Caffeine is the most widely used psychoactive substance in the world [69]. Most of the caffeine consumed comes from dietary sources such as coffee, tea, cola drinks and chocolate. The most notable behavioral effects of caffeine occur after low to moderate doses (50–300 mg) and are increased alertness, energy and ability to concentrate. Moderate caffeine consumption leads very rarely to health risks [19, 40, 109]. Higher doses of caffeine rather induce negative effects such as anxiety, restlessness, insomnia and tachycardia, these effects being seen primarily in a small portion of caffeine-sensitive individuals. On the other hand, caffeine was considered in one study as a potential drug of abuse [71] and more recently described as “a model drug of abuse” [99]. Finally, based on a review of science and clinical data, the possibility that caffeine withdrawal but not abuse and dependence should be added to diagnostic manuals has been considered in the United States [107]. The present paper will review the available data on coffee and caffeine consumption, caffeine dependence, withdrawal and reinforcement, and try to assess in which respect caffeine differs from drugs of abuse such as amphetamines, cocaine and morphine. It will also consider the reasons why caffeine could be considered a potential drug of dependence.

2. Coffee and caffeine consumption

2.1. Coffee consumption

After having been limited to the Arab world until the fifteenth century, coffee consumption reached the European world during the sixteenth century and rapidly spread throughout Europe [42]. According to recent surveys, consumption of coffee varies greatly among the different...
countries. The highest consumption (more than 10 kg/person/year) is encountered in all Scandinavian countries plus Austria and the Netherlands. In most western European countries, as well as in Brazil and Costa Rica, coffee consumption ranges from 6–9 kg/person/year. The lowest consumption (less than 5 kg/person/year) occurs in the United States, Italy, Algeria, Nicaragua and Paraguay [42, 70].

The content of caffeine per cup of coffee also varies largely according to the size of the serving, the mode of preparation of the coffee (boiled, filter, percolated, espresso or instant), and the type of coffee used (Arabica or Robusta) [42, 44]. Indeed, as can be seen in Table 1, the size of a cup of coffee can range from 50–190 ml and the standard content of caffeine in a cup of coffee can be as low as 19 mg/cup for instant coffee and reach a maximum value of 177 mg/cup in boiled coffee.

From these data, the caffeine content of a cup of coffee ranges from 0.7–1.1 mg/ml for boiled or filter coffee, 0.6–3.3 mg/ml for espresso and 0.2–0.6 mg/ml (eventually up to 1.0 mg/ml) in instant coffee [42].

Most of the coffee consumed throughout the world is Arabica. In most countries, Arabica represents 70%–100% (100% in Finland and Sweden) of the whole coffee consumed. The only exceptions are France, Italy, Portugal and the UK, where Robusta represents 42%–70% of the whole coffee consumption [42, 44]. The average content of caffeine is about twice as high in Robusta as in Arabica coffee. Indeed, the content of caffeine, expressed as percent of dry weight, ranges from 0.9%–1.2% in green Arabica beans and averages 1.3% in roasted Arabica beans. In Robusta coffee, the content of caffeine is 1.6%–2.4% and 2.0% of the dry weight for green and roasted beans, respectively. As a consequence, in a standard 150 ml cup, the content of caffeine ranges from 71–120 mg/cup for Arabica coffee and from 131–220 mg/cup for Robusta [42, 191, 192].

World coffee consumption is increasing. The average consumption of coffee in 1990 ranged from 1.41 cups/day in Japan, to 1.73 cups/day in the United States and 3.87 cups/day in Germany [42]. In the United States, coffee consumption (numbers of cups/person/day) decreased in 1986 and has not changed since then. In Japan, coffee consumption has been constantly increasing over the last 10 years, while in Germany the consumption has been stable over the same period [42]. The results of a survey performed in France [173] indicate that four attitudes are positively linked to the quantity of coffee consumed. They are, in decreasing order of importance, the need for a stimulant, the preference for strong coffee, the knowledge of coffee, and the preference for the coffee roasting shop.

### 2.2. Caffeine consumption

Caffeine is present in a number of dietary sources consumed worldwide, i.e. tea, coffee, cocoa beverages, candy bars, and soft drinks. The content of caffeine of these various food items ranges from 71–220 mg/150 ml for coffee, to 32–42 mg/150 ml for tea, 32–70 mg/330 ml for cola and 4 mg/150 ml for cocoa [44]. Caffeine consumption from all sources can be estimated as 76 mg/person/day but reaches 210–238 mg/day in the United States and Canada and more than 400 mg/person/day in Sweden and Finland where 80%–100% of the caffeine intake comes only from coffee [16, 17, 44, 191, 192]. In the UK, the consumption is as high as in the later two countries but 72% is represented by tea [44]. According to the recent survey of Barone and Roberts [17], the daily intake of caffeine from all sources in the United States is estimated at 3 mg/kg/person, two thirds of it coming from coffee in subjects aged more than 10 years. If only consumers are taken into account, the daily caffeine consumption reaches a value of 2.4–4.0 mg/kg (170–300 mg) in a 60–70 kg individual. In children, the soft drinks represent 35%, chocolate foods and beverages 35%–40% and tea 6%–10% of the total caffeine intake [51].

### 3. Caffeine absorption and pharmacokinetics

Caffeine absorption from the gastrointestinal tract is rapid and reaches 99% in humans about 45 min after ingestion [13, 21–23, 132]. Caffeine absorption is also complete in animals [10, 11]. Pharmacokinetics are comparable after oral or intravenous administration of caffeine in humans and animals, leading to superimposable plasma curves [13].

Peak plasma caffeine concentration is reached between 15–120 min after oral ingestion in humans and equals 8–10 mg/l for doses of 5–8 mg/kg [14, 23]. For doses lower than 10 mg/kg, the caffeine half-life ranges from 0.7–1.2 h in rats and mice, 3–5 h in monkeys [24] and 2.5–4.5 h in humans [12]. There are no differences in the caffeine half-life in young and elderly humans [22]. Conversely, the caffeine half-life is increased during the neonatal period due to the lower activity of cytochrome P-450 [7] and to the relative immaturity of some demethylation and acetylation pathways [9, 32]. The half-life of caffeine is about 80 ± 23 h for the full-term newborn infant [8, 125] and can be over 100 h in premature infants [154]. Thereafter, the half-life of caffeine decreases exponentially with postnatal age to reach 14.4 h and 2.6 h in 3–5 and 5–6 month-old infants, respectively [2, 152, 154, 156]. The clearance of caffeine is low in one-month-old infants (31 ml/kg/h), but increases to

<table>
<thead>
<tr>
<th>Mode of preparation</th>
<th>Volume of serving</th>
<th>Caffeine content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiled</td>
<td>150–190 ml</td>
<td>111–177 mg/cup</td>
</tr>
<tr>
<td>Filter</td>
<td>50–190 ml</td>
<td>28–161 mg/cup</td>
</tr>
<tr>
<td>Espresso</td>
<td>50–150 ml</td>
<td>74–99 mg/cup</td>
</tr>
<tr>
<td>Percolated</td>
<td>150–190 ml</td>
<td>55–88 mg/cup</td>
</tr>
<tr>
<td>Instant</td>
<td>50–190 ml</td>
<td>19–34 mg/cup</td>
</tr>
</tbody>
</table>

### Table 1 Content of caffeine in a cup of coffee according to the mode of preparation (data from Refs. [36, 38])
a maximum value of 331 ml/kg/h at 5–6 months, compared with 155 ml/kg/h in adult humans [7]. In adult males, the caffeine half-life is reduced by 30%–50% in smokers, compared with nonsmokers [90, 111, 137], while it is approximately doubled in women taking oral contraceptives [155] and largely prolonged (up to 15 h) during the last trimester of pregnancy [3, 28, 118].

Caffeine is metabolized through liver biotransformation into dimethylxanthines, dimethyl and monomethyl uric acids, trimethyl- and dimethyl-allantoin, and uracil derivatives. The metabolic pathways show multiple and separate demethylation, C-8 oxidation and uracil formation in humans and rodents, that occur predominantly in liver microsomes. The main difference between rodents and humans is that, in the rat, 40% of the caffeine metabolites are trimethyl derivatives, while they do not exceed 6% in humans. Conversely, in humans, the 3-methyl demethylation, leading to the formation of paraxanthine, represents 72%–80% of caffeine metabolism [12, 13].

4. Mechanism of action of caffeine

The effect of caffeine on the release of intracellular calcium and as an inhibitor of cyclic nucleotide phosphodiesterases has been mainly shown in vitro at 500 micro- or milli-molar concentrations, respectively, i.e. at doses higher than those usually achieved by human consumption [139, 140] and cannot therefore account for most of the physiological effects of caffeine. One exception is the respiratory-stimulant effect of caffeine that appears to be prominently mediated by the inhibition of type IV phosphodiesterase [102]. In fact, it is now widely accepted that the main mechanism of action of caffeine occurring at circulating concentrations achieved after the consumption of one or two cups of coffee, is the antagonism at the level of adenosine receptors [62, 63, 139, 140]. Indeed, in animals, most pharmacological effects of adenosine in the brain can be suppressed by relatively low concentrations of circulating caffeine, i.e. less than 100 μM, which are attained after the consumption of one to three cups of coffee. Adenosine decreases the firing rate of neurones and exerts an inhibitory effect on synaptic transmission and on the release of most neurotransmitters, while caffeine increases the turnover of many neurotransmitters, including monoamines and acetylcholine [139, 140].

The A1 and A2a adenosine receptors are the subtypes that are primarily involved in the effects of caffeine, while the A2b and A3 receptors play only a minor role. The A1 receptors are negatively linked to adenyl cyclase, while the A2a receptors are positively linked to the enzyme. Adenosine A1 receptors are widely distributed throughout the brain with high levels in the hippocampus, cerebral and cerebellar cortex, and thalamus [43, 54, 77]. Conversely, A2a receptors are almost exclusively located in the striatum, nucleus accumbens and olfactory tubercle [110, 149, 153]. In the latter regions, A2a receptors are coexpressed with enkephalin and dopamine D2 receptors in the same kind of striatal neuronal cells [58, 149, 171]. There is direct evidence for a central functional interaction between adenosine A2a and dopamine D2 receptors. Indeed, the administration of adenosine A2a receptor agonists decreases the affinity of dopamine binding to D2 receptors in striatal membranes [57]. The interaction between adenosine A2a receptors and dopamine D2 receptors in the striatum might underlie some of the behavioral effects of methylxanthines. By antagonizing the negative modulatory effects of adenosine receptors on dopamine receptors, caffeine leads to the inhibition and blockage of adenosine A2 receptors, leading to a potentiation of dopaminergic neurotransmission [56, 65, 158]. The latter interaction is very interesting since it could explain the adenosine receptor antagonists-induced increase in behaviors related to dopamine [41], such as, e.g. caffeine-induced rotational behavior [67].

5. Addiction and drug dependence

Drug dependence has been defined as ‘a pattern of behavior focused on the repetitive and compulsive seeking and taking of a psychoactive drug’ [92]. However, it is necessary to demonstrate psychoactive effects to differentiate drug dependence from other habitual or controlled behaviors, such as the daily ingestion of some types of medication like aspirin or vitamins. Moreover, it appears necessary to demonstrate that the drug is reinforcing its own ingestion. Therefore, the following section will consider the criteria used for the definition of dependence.

The recent diagnostic manuals from the World Health Organization (WHO) [197] and the American Psychiatric Association (APA) [4, 5] proposed a new set of criteria for dependence. The diagnosis of dependence requires the fulfillment of three (non specified) of the six WHO [196] or seven APA [4, 5] criteria. The seven criteria of dependence as proposed by the APA [5] in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.) are: (i) tolerance (not specified for severity); (ii) substance-specific withdrawal syndrome (psychic or physiological, not specified for severity); (iii) substance is often taken in larger amounts or over a longer period than intended; (iv) persistent desire or unsuccessful efforts to cut down or control use; (v) a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance; (vi) important social, occupational or recreational activities given up or reduced because of substance use; and (vii) use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. The six criteria proposed by the WHO [197] differ only slightly from those of the APA, mainly by a different sequence, slightly different formulations and the combination of criteria (v) and (vi) into a single one. The only possibility
to differentiate between substances that can lead to dependence is to classify them according to the number of criteria met and specify for severity of symptoms and frequency of occurrence.

The possible dependence on caffeine has been considered by several groups for over a decade [71, 78, 83, 84, 88, 92, 93, 186] and caffeine has even been postulated as a ‘potential model of drug of abuse’ [99]. In two recent studies using the criteria cited above, a dependence on caffeine was shown in a subset of the general population. As a result of a random telephone survey in Vermont, Hughes et al. [106] showed that 14% and 3% of the 166 caffeine users interviewed met the criteria for moderate and severe caffeine dependence, respectively. After telephone screening performed on 99 subjects in the United States, Strain et al. [187] found 16 individuals that fulfilled four out of the seven criteria cited above, and were thus considered dependent on caffeine. The criteria met were criteria (i), (ii), (iv) and (vii) of DSM-IV. Criteria (iii), (v) and (vi) were excluded because they do not apply to a substance widely available and culturally accepted. The dependence was not related to the daily caffeine intake which ranged from 129–2548 mg/day. The median daily caffeine intake for the caffeine-dependent individuals was 360 mg and about 40% of them had a daily caffeine intake of 300 mg or less [187]. However, in spite of the absence of current psychiatric disorders at the time of the study in most of the individuals (14 out of 16), 11 of the 16 persons diagnosed with ‘caffeine dependence’ had a history of psychiatric disorders, mainly substance abuse disorders (10 subjects) and mood disorders (seven subjects). The prevalence of these disorders is higher than that encountered in the general population, i.e. 50% [117]. Moreover, the tendency to an association between caffeine, alcohol, and nicotine consumption [122], as well as between mood disorders and nicotine dependence has been previously reported [29, 116].

Therefore, to try to assess in which respect caffeine should or should not be considered a drug of dependence, in the present review, the consequences of coffee and caffeine consumption on various criteria, possibly leading to the diagnosis of dependence, will be considered. Among the seven criteria for drug dependence that have been cited above, the four main factors to consider are withdrawal, tolerance, reinforcement and dependence.

6. Caffeine withdrawal

6.1. Caffeine withdrawal in animals

There are several reports showing caffeine withdrawal signs in rats, cats and monkeys. They include decreases in locomotor activity [59, 98], operant behavior [31, 33, 136], and in the reinforcement threshold for electrical brain stimulation [136]. Other studies have reported changes in the time spent in various phases of slow wave sleep [180] and avoidance of a preferred flavor when the latter was paired with caffeine abstinence [193]. The severity of caffeine withdrawal depends on the dose, and decreases in locomotor activity do not appear when caffeine doses lower than 67 mg/kg/day are substituted by water [59, 98]. The length of the decrease in locomotor activity depends also upon the dose of caffeine and the duration of the treatment before the substitution by water [59, 98]. The latency to the onset of caffeine withdrawal effects usually occurs within 24 h, and peaks around 24–48 h [31, 33, 59, 98, 136, 180, 193]. The caffeine withdrawal-induced behavioral changes usually last a few days [85], except for the sleep-related signs that have been shown to last up to 30 days after the onset of caffeine withdrawal [180].

6.2. Characterization of withdrawal symptoms in humans

Caffeine withdrawal translates into typical symptoms. The most often reported are headaches, feelings of weariness, weakness and drowsiness, impaired concentration, fatigue and work difficulty, depression, anxiety, irritability, increased muscle tension, occasionally tremor, and nausea and vomiting, as well as withdrawal feelings [83, 105, 140, 164, 177, 186, 187]. Withdrawal symptoms generally begin about 12–24 h after sudden cessation of caffeine consumption and reach a peak after 20–48 h. However, in some individuals, these symptoms can appear within only 3–6 h and last for one week [16, 108, 124, 140]. Withdrawal symptoms do not relate to the quantity of caffeine ingested daily [86–88, 96, 97, 107, 187], e.g. the recent study of Strain et al. [187] showed that withdrawal symptoms occur in individuals who daily consume anything from 129–2548 mg of caffeine. In the last decade, two studies [107, 187] suggested that caffeine withdrawal symptoms (but not abuse or dependence) should be added to the list of diagnoses recognized by the American Health System (DSM-IV and ICD-10).

There is a strong positive correlation between caffeine consumption, fasting and headaches before and after surgical procedures. For every increase in the usual daily consumption of 100 mg of caffeine (about a cup of coffee), the risk of headache immediately before and after surgery is increased by 12% and 16%, respectively, and correlates also with the duration of fasting [55, 144]. The risk of headaches is reduced in individuals who drink caffeine or get substitutive caffeine tablets on the day of the surgery [89, 195, 196]. Therefore, it was advised by three studies that the numerous healthy patients who drink caffeine-containing beverages daily and are undergoing minor surgical procedures should be permitted to ingest preoperative caffeine [144, 195, 196]. In their most recent study, Weber et al. [196] also showed that in the population selected, 40%–48% of the patients already suffered regular headaches (at least weekly) at the time they underwent surgery. Moreover, there is a relationship between caffeine withdrawal, the development of headaches and changes in cerebral blood flow. The cerebral
blood flow velocities are increased during withdrawal headaches, significantly decreased within 30 min after caffeine intake in all subjects and return to baseline values after 2 h [39]. This recent study confirms several previous ones that suggested that increased blood volume may be involved in caffeine withdrawal headaches [48, 94, 133, 194]. Caffeine withdrawal symptoms were even reported in newborns whose mothers were heavy coffee drinkers during pregnancy. The infants displayed irritability, high emotionality and, eventually, vomiting. Symptoms begun at birth but spontaneously disappeared after a few days [134].

Recently, Smith [181] reported that in a population of 144 students who discriminated caffeine only at chance level, there was no difference in the frequency of headaches between the group in which caffeine was withdrawn and the one receiving caffeinated coffee over the 3 day protocol. This effect could be interpreted as an expectancy effect that might not have occurred in other studies where subjects were able to discriminate caffeine.

6.3. Relief of abstinence symptoms by caffeine

Caffeine withdrawal symptoms disappear soon after absorption of caffeine. This effect is strongly linked to the psychological satisfaction related to the ingestion of caffeine; this is especially true for the first cup of the day. The potential reversal of caffeine withdrawal-induced headaches and other symptoms by the absorption of caffeine alone has been known for over 50 years and has been shown repeatedly [48, 73, 74, 86, 103]. The occurrence of headaches on substitution of caffeinated by decaffeinated coffee predicts subsequent caffeine self-administration [103]. Caffeine content influences coffee consumption [86, 87, 121] and the beneficial effects of caffeine consumption on mood or alertness seem to incite people to drink coffee or caffeine-containing beverages [123, 164]. Heavy consumers of coffee show a preference for coffee that contains caffeine, while those who used to drink decaffeinated coffee will choose either decaffeinated or caffeine-containing coffee [78, 185]. When subjects are categorized between caffeine choosers and nonchoosers, caffeine choosers tend to report both positive subjective effects of caffeine (stimulant and positive effects on mood and vigilance) as well as negative subjective effects of placebo (headache and fatigue), while caffeine nonchoosers tend to report negative effects of caffeine (primarily anxiety and dysphoria) [53, 179, 185].

7. Tolerance to the effects of caffeine

Tolerance to a drug refers to an acquired change in responsiveness of a subject repeatedly exposed to the drug and can be considered in two ways. First, tolerance might indicate that the dose necessary to achieve the desired euphoric or reinforcing effects will increase with time, thus inciting people to gradually consume more of the drug. Second, tolerance to the aversive effects of high doses of the drug may occur, hence leading people to consume higher doses of the drug over time.

Tolerance to many behavioral effects of caffeine occurs in mice, cats and squirrel monkeys chronically treated with methylxanthines (for review, see [85, 100]). Thus, tolerance to caffeine-induced locomotor stimulation [1, 35, 59–61, 98, 100], cerebral electrical activity [35, 95, 98], reinforcement thresholds for electrical brain stimulation [136], schedule-controlled responding maintained by presentation of food and electric shock [100, 115], and thresholds for caffeine- [199] or NMDA-induced seizures [68] has been described. The development of tolerance to caffeine in animals is rapid, usually insurmountable, shows cross-tolerance with other methylxanthines but not with psychomotor stimulants such as amphetamines and methylphenidate [60, 61, 98, 100]. On the first two days after caffeine discontinuation, depression of locomotor activity is noted with a return to baseline values on the third day, consistent with a withdrawal syndrome [59, 60, 98]. Although the exact mechanism underlying the development of tolerance to caffeine remains unclear, tolerance to behavioral effects of caffeine in animals does not seem to involve adaptive changes in adenosine receptors [68, 101] and may rather result from compensatory changes in the dopaminergic system as a result of chronic adenosine receptor blockage [66].

In humans the tolerance to some physiological actions of caffeine has been shown to occur. This is the case for the effect of caffeine on blood pressure and heart rate [6, 45, 165, 169, 175], diuresis [50], plasma adrenaline and norepinephrine levels, and renin activity [165], that usually develops within a few days. Tolerance to some subjective effects of caffeine, such as increases in tension-anxiety, jitteriness/nervousness, activity/stimulation/energy, and the strength of drug effect [53] was recently shown to occur. Conversely, although tolerance to the enhancement of arithmetic skills by caffeine was recently shown [169], there is only limited evidence for tolerance to caffeine-induced alertness and wakefulness [38, 76, 96, 97]. These effects are paralleled by the lack of tolerance of cerebral energy metabolism to caffeine, since an acute administration of 10 mg/kg caffeine induces the same metabolic increases whether the rats have been exposed to a previous daily chronic treatment by caffeine or saline for 15 days [138]. These data show that every single exposure to caffeine is able to produce cerebral stimulant effects and this is especially true in the areas that control locomotor activity (caudate nucleus) and the structures involved in the sleep-wake cycle (locus coeruleus, raphe nuclei and reticular formation) [138].

In humans, sleep seems to be the physiological function most sensitive to the effects of caffeine, as detailed in a recent review [182]. Generally, more than 200 mg caffeine are needed to affect sleep significantly. Caffeine has been shown to prolong sleep latency, shorten total sleep duration but to preserve the dream phases of sleep. It is not clearly established yet whether or not the difference in the
sensitivity to the effects of coffee on sleep could be attributable to tolerance. According to some studies, this difference could rather reflect the interindividual sensitivity to caffeine, possibly related to differences in the rate of caffeine metabolism [126, 190]. Indeed poor sleepers are reported to metabolize caffeine at a lower rate and four out of the 10 subjects of the study had elimination half-lives exceeding 4.8 h [190]. The variability in the subjects response from one night to the next should also be taken into account [76, 96, 97, 127]. Nevertheless, there are some indications of a development of tolerance to sleep disturbances related to caffeine intake since heavy coffee drinkers appear to be less sensitive to caffeine-induced sleep disturbances than light coffee drinkers [38]. Likewise, tolerance to sleep latency and quality to caffeine has been shown to develop over 2 days of testing in one study [200] and 7 days in another [25]. However, the tolerance is not complete and the sleep efficiency remains below 90% of the baseline value after 7 days of caffeine treatment [25].

Thus, tolerance to some of the effects linked to regular consumption of coffee seems to occur, especially in animals. In humans, the data are less conclusive and this may underlie individual differences in the susceptibility and tolerance to caffeine-induced effects. Moreover, mechanisms of tolerance may be overwhelmed by the nonlinear accumulation of caffeine and its main metabolites in the human body when caffeine metabolism becomes saturable under multiple dosing conditions [45, 46].

### 8. Discrimination and reinforcement of caffeine in humans

#### 8.1. Discrimination of caffeine

Human subjects are able to discriminate caffeine against placebo both when offered in capsules or in coffee. Doses of 300 mg or higher are usually more easily detected and mainly recognized by their negative effects of jitteriness, anxiety or nervousness, whereas the lower doses are detected by their lack of effect or by caffeine withdrawal symptoms. However, several studies have failed to demonstrate behavioral effects of caffeine at doses below 200 or 300 mg, i.e. amounts corresponding to the ingestion of two to three cups of coffee [18, 69]. Doses in the range of 100 mg, which closely approach the caffeine content of a normal serving are detected poorly or at chance level only in one study [185], by 30% or 60% of the individuals according to two other studies, respectively [86, 103]. However, in most of these studies, subjects were not withdrawn for a prolonged period from their habitual daily amounts of caffeine and thus may have been tolerant.

In fact, doses of caffeine below 100 mg neither induce feelings of withdrawal nor negative effects, have rarely been shown to alter self-reports of mood or performance and are usually preferred by moderate coffee drinkers [104]. One study recently showed discrimination of caffeine at doses as low as 10 mg for one individual, 18 mg for three subjects, and 56 mg for three others [82]. That study involving the authors themselves was replicated with subjects less informed of the potential effects of the drugs under study. Data in the same range as in the previous study were obtained with caffeine discrimination in one subject at 18 mg of caffeine, in one at 32 mg, in two at 56 mg and in four at 100 mg caffeine. The authors suggested that in specific individuals, caffeine could be considered to affect mood at doses lower than those previously reported [178]. Indeed, some groups were able to show enhanced auditory vigilance and reaction time at 75 mg [36], 64 mg [127], or even 32 mg [128] of caffeine. It seems that the effects of caffeine are utilized consciously or unconsciously by the various individuals in the management of mood state, relevant to the context of drink choice [64]. The discrimination of low doses of caffeine is not related to the taste of caffeine since at the dose of 100 mg, subjects are not able to reliably differentiate decaffeinated coffee plus lactose from decaffeinated coffee plus 100 mg of caffeine [80]. Conversely, at higher doses, caffeine could be detected in coffee as high concentrations relate directly to coffee bitterness [79].

#### 8.2. Reinforcing effects of caffeine

Reinforcing efficacy of a drug refers to the relative efficacy in establishing or maintaining a behavior on which the delivery of the drug is dependent. In animals, intravenous self-administration of caffeine has been studied after the implantation of venous catheters allowing them by pressing a lever to self-administer the drug and assess behavioral reinforcement [84]. In four studies, caffeine was shown to be self-injected in all animals [47, 49, 81, 84], while three showed that only a limited subset (25%–33%) of the animals self-administered caffeine [15, 37, 172]. A sporadic pattern of caffeine self-administration, characterized by periods with high rates of self-injection alternating with periods of rather low intake was found in nonhuman primates [47, 81, 84]. Thus, although caffeine seems to be able to act as a reinforcer in some conditions, there is a marked difference between caffeine and classical drugs of abuse, such as amphetamines and cocaine, that maintain self-administration across species and conditions [81, 159]. Recently, caffeine was shown to be able to reinstate extinguished cocaine-taking behavior in rats. This effect was more marked when caffeine was given one day, rather than four days, following the last cocaine self-administration session. Thus, extended withdrawal is able to increase the priming effects of caffeine [170, 198]. However, it must be remembered that these animal studies use intravenous self-administration while human caffeine consumption is always by oral route and it is known that the former mode of administration is by far more addictive than the latter one [93]. Thus, caffeine dose does not appear to be a very robust reinforcer in animals.
In humans, the widely recognized behavioral stimulant and mildly reinforcing properties of caffeine are probably responsible for the maintenance of caffeine self-administration, primarily in the form of caffeinated beverages, such as coffee, tea and cola [84, 140]. In some studies, the choice of caffeine has been shown to be more potently controlled by avoiding withdrawal than by its positive effects [166, 175], while other data support the hypothesis that the true performance-enhancing effects of caffeine are responsible for its self-administration [167]. Most data showed that caffeine reinforcement occurs in 100% of heavy caffeine consumers (1020–1530 mg/day) that also had histories of alcohol or drug abuse [78–80]. For moderate caffeine users (128–595 mg/day), caffeine reinforcement occurs in about 45% [88, 103, 104, 147, 148] to possibly 80%–100% of the subjects [52, 179].

Caffeine reinforcement varies with the dose. Doses of caffeine encountered in tea and coffee are high enough to act as reinforcers, since people look for them in case of withdrawal symptoms [103]. Indeed, a dose of 25–50 mg caffeine per cup of coffee acts as a reinforcer, while increasing doses beyond 50 or 100 mg tends to decrease the choice of caffeine or the frequency of caffeine self-administration [84], and high doses of caffeine (400–600 mg in a single dose) are avoided [86]. Caffeine reinforcement relates also to withdrawal syndromes occurring after coffee cessation. Indeed, subjects that consistently suffer from caffeine withdrawal headaches increase their chance to select caffeinated coffee (containing 100 mg caffeine) by 2.6 [105]. Moreover, the choice of caffeine seems to be more potently controlled by avoiding withdrawal than it is by its positive effects [176].

Recently, Bickel et al. [20] reviewed 16 studies dealing with the behavioral economics paradigm for the study of drug abuse. Increasing consumption of a fixed price item when another one becomes more expensive indicates a substitutive function and appears clearly with opiates, cocaine and phencyclidine, but not with caffeine. These data confirm the already-known fact that caffeine is less reinforcing than amphetamines and related psychomotor stimulants [34, 36, 112, 120, 185].

8.3. Reinforcing effects of caffeine-containing drinks unrelated to caffeine

The conditions under which caffeine functions as a reinforcer are still not clearly understood. However, the possible reinforcing effects of coffee unrelated to caffeine, but related to its smell, taste and social environment usually accompanying coffee consumption should not be totally neglected in the every day motivations for caffeine-containing or caffeine-free coffee consumption. Indeed, in subjects with a habitual coffee consumption of 4–10 cups/day (mean intake 6 cups/day) and switched without a withdrawal period to the consumption of 600 mg of caffeine either in tablets containing 50 mg of caffeine each or decaffeinated instant coffee for three days, the desire for coffee in the next three days largely increased in the group given caffeine tablets but remained unchanged in the group given decaffeinated instant coffee, although the latter group experienced marked symptoms of caffeine withdrawal [97].

The question of whether the taste of coffee and caffeine may influence its intake is still a matter of debate. If water containing caffeine is given chronically to rats between 29 and 40 days of postnatal life, rats exposed to caffeine as adults will drink more caffeinated water than tap water. Likewise the previous administration of an adenosine agonist increases caffeine intake. Thus, it seems that caffeine intake could be at least partly related to its pharmacological properties, although the influence of taste cannot be eliminated [143]. Coffee and caffeine would in fact have two components, an appetitive and an aversive one. The absorption of low quantities of caffeine could favor the appetitive effect of caffeine [193], whereas higher quantities could exacerbate its aversive effects [183]. In man, the gustatory response to caffeine is not influenced by previous exposure to a series of methylxanthines or adenosine [30, 135] or by caffeine deprivation [27]. However, the taste of coffee is an important aspect of caffeine consumption and subjects prefer caffeine in coffee to caffeine in capsules [80].

Another possibility is that caffeine is a constituent of coffee and tea which are liked for reasons independent from their caffeine content. Thirst could be one factor but is probably not the main one involved in the consumption of tea or coffee, while it could contribute more to the consumption of soft drinks. Liking the sensory properties of tea and coffee can also be related to the nutritional benefit derived from the milk, cream and/or sugar added to the beverage. The last possibility is the influence of situational conditions on mood that can play an important role in reinforcing preferences for specific foods and beverages. Indeed, coffee and tea are often consumed in social contexts and during breaks from work [166]. Therefore, the influence of caffeine on the consumption of tea, coffee or soft drinks may be relatively subtle and depend both on the accumulated dose over the day and the mood state in which it is consumed. For example, if an individual is already quite stimulated, the ingestion of a caffeine-containing beverage may lead to unpleasant effects. Indeed, it was shown recently that, at least in some individuals, the choice to drink coffee is influenced by the interaction between the mood state before coffee and the effects anticipated based on the content of caffeine in the drink [26, 64].

9. Molecular mechanisms underlying drug dependence

The molecular mechanisms underlying reinforcement and drug dependence were recently reviewed [174] and the critical role of the mesolimbic dopamine system emphasized. The mesolimbic dopamine system consists of the dopaminergic neurons originating in the ventral tegmental
area and ending in the nucleus accumbens. Rats self-administer amphetamines and dopamine directly into the nucleus accumbens and the ventral tegmental area as well as in other brain regions connected to the mesolimbic dopaminergic system such as the cerebral cortex, hippocampus and lateral hypothalamus [114, 119, 174].

The nucleus accumbens that plays a central role in the mechanism of drug dependence is functionally and morphologically divided into a core and a shell part. The medioventral shell part is related to the limbic ‘extended amygdala’ assumed to play a role in emotional, motivational and reward functions, whereas the laterodorsal core part regulates somatomotor functions [91]. The specificity of cocaine, amphetamines, morphine, alcohol, Δ⁹-tetrahydrocannabinol, and also nicotine, is to selectively activate the dopaminergic neurotransmission in the shell of the nucleus accumbens as compared with the caudate nucleus [159, 160, 188], a property that has been related to the strong addictive properties of these drugs [119, 174]. Dopamine D2 receptors are necessary for opiate rewarding, since in transgenic mice lacking these receptors, the motivational component of drug addiction is specifically suppressed while the behavior oriented at food rewarding is maintained [131]. Likewise, the dopamine transporter is an obligatory target of cocaine and amphetamines, as these psychoactive drugs have no effect on dopamine release and uptake in mice lacking the dopamine transporter [72]. Conversely to the drugs of abuse that selectively lead to a release of dopamine in the shell of the nucleus accumbens [159, 160, 188], caffeine increases dopamine release in the caudate nucleus [145, 146], which relates to the stimulatory properties of caffeine on locomotor activity [139, 140], but does not induce any release of dopamine in the shell of the nucleus accumbens when injected at doses ranging from 0.5–5.0 mg/kg [189]. This data is consistent with the low addictive potential of caffeine. However, at the latter doses, caffeine stimulates the release of dopamine in the prefrontal cortex, the terminal area of the mesolimbic dopaminergic system which is consistent with its reinforcing and psychostimulant properties [189].

10. Effects of drugs of dependence and caffeine on cerebral functional activity

Amphetamines, cocaine, and also nicotine, induce parallel increases in the release of dopamine and the rates of cerebral glucose utilization and blood flow in the nucleus accumbens [129, 160–163, 184], with a specific activation of the shell of the nucleus, while there are no changes in these parameters in the core of the nucleus accumbens [150, 160, 162, 163, 184]. Conversely, the acute administration of caffeine does not lead to a release of dopamine and a metabolic increase in the shell of the nucleus accumbens at doses ranging from 1–5 mg/kg in the rat. The caffeine-induced metabolic increase in the shell of the nucleus accumbens can only be recorded after the administration of 10 mg/kg of caffeine, at which dose rates of cerebral glucose utilization are simultaneously increased in the core of the nucleus accumbens ([138, 141] and unpublished personal data), which differs from the specific metabolic changes in the shell of the nucleus accumbens recorded with addictive drugs [160, 162, 184]. Moreover, the dose of 10 mg/kg of caffeine at which a metabolic increase is recorded in both the shell and the core of the nucleus accumbens is about five times higher than the mean human daily caffeine consumption [44]. In addition to the metabolic increase in both parts of the nucleus accumbens, that dose of caffeine leads to widespread cerebral metabolic increases recorded in most structures of the extrapyramidal motor system, many limbic and thalamic regions, as well as several areas of the cerebral cortex [138, 141]. Conversely, the doses of addictive drugs that elicit the increase in functional activity in the shell of the nucleus accumbens are rather low and activate only a very limited number of brain regions together with the latter structure, such as the caudate nucleus in the case of amphetamines, for example [163].

Taken together, these data show that caffeine increases cerebral functional activity in the shell of the nucleus accumbens only at doses at which it already activates numerous other brain regions. In fact, caffeine primarily acts on the extrapyramidal motor system leading to a release of dopamine in the caudate nucleus [145, 146] and on cerebral structures related to the sleep-wake cycle such as the reticular formation, raphe nuclei and locus coerules [138, 141]. These data are in good accordance with the facilitated motor output [108, 130], the increase in wakefulness reported in humans after caffeine ingestion [108], and the caffeine-induced dopamine release in the caudate nucleus and the prefrontal cortex [145, 146, 188]. Conversely, the effects of amphetamines, cocaine and nicotine on the neural substrates underlying addiction are quite specific and occur at doses that do not usually lead to the activation of many other brain regions [160, 162, 184]. Moreover, cocaine, amphetamines and nicotine induce the expression of the immediate early gene c-fos in the nucleus accumbens and structures related to the ‘extended amygdala’ while the expression of c-fos is only increased in the caudate nucleus after caffeine [113, 151].

Thus, the effect of caffeine on the dopamine-mediated brain reward system occurs only at high doses, i.e. 10 mg/kg in rats that correspond to the ingestion of 200–300 mg of caffeine in a 70 kg individual and lead to a plasma concentration of 13–16 μg/ml [138]. This dose is higher than those necessary to activate the motor system and the sleep-wake cycle and induces a widespread increase in rates of cerebral energy metabolism [138, 141] that also reflects the numerous side effects of the ingestion of rather high doses of caffeine and is already related to somewhat aversive effects.
11. Conclusion

The objective of the present review was to analyze the possible dependence potential of coffee and/or caffeine. Specifically, three main factors were considered: withdrawal, tolerance, and reinforcement. In addition, the molecular basis for the action of the classical drugs of dependence and of caffeine was considered.

A withdrawal syndrome to caffeine has been described which does not seem to relate to the quantity of caffeine ingested daily. Tolerance to behaviorally-induced effects of caffeine occurs in animals. In humans, tolerance to some subjective effects of caffeine as well as partial tolerance to sleep seems to occur, at least in some individuals. Caffeine does not act consistently as a reinforcer in animals and obviously in a more limited range of conditions than do classiscal drugs of dependence. In humans, the reinforcing stimuli functions of caffeine are limited to low or rather moderate doses that are usually present in a classical serving of coffee or soft drink.

When considering the molecular basis for drug dependence, it appears that the classical drugs of abuse such as amphetamines, cocaine and nicotine induce specific increases in dopamine release and functional activity in the shell of the nucleus accumbens, the key structure for reward, motivation and addiction. Conversely, caffeine does not induce the release of dopamine and increase glucose utilization in the shell of the nucleus accumbens. Glucose utilization in the latter structure increases only at rather high doses that are usually avoided by the general population, probably since they activate the whole brain energy metabolism. Caffeine acts as amphetamines and cocaine on the dopaminergic system. Nicotine activates other brain areas, but shares with amphetamines and cocaine the property of specifically affecting the release of dopamine in the nucleus accumbens. Other drugs, such as phenylcyclohexylamine, barbiturates and benzodiazepines, that can create withdrawal, reinforcement and tolerance, do not clearly share dopaminergic mechanisms of action with amphetamines, nicotine and cocaine.

Usually, the consumption of caffeine occurs by the oral route and is gradual over the day, and the delay in the absorption of caffeine reduces the likelihood of a strong dependence, unlike drugs of abuse that are most often administered via the intravenous or inhaled form. When caffeine is administered intravenously to subjects with histories of stimulant drug abuse, the methylxanthine increases dose-dependently ratings of positive mood (i.e. liking the drug) and the frequency of identification to a stimulant like cocaine [168]. Likewise, cocaine specifically increases cerebral glucose utilization when given to rats by the intravenous route, but does not do so when given intraperitoneally [161]. A typical example of the difference in the addictive effects of a psychoactive stimulant is the case of nicotine, which is highly addictive when inhaled in the form of cigarettes while it is used as a gum or a transdermal patch to reduce its addictive potential and help people to progressively quit smoking [142, 157]. However, it must be remembered that drug dependence can occur in some cases by the oral route, with alcohol, oral amphetamines, barbiturates and benzodiazepines.

In conclusion, it appears that, although caffeine fulfills some of the criteria for drug dependence, the relative risk of addiction of caffeine is quite low and, as reported previously, is the lowest among seven drugs or drug classes considered [75].

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