Influence of repeated exposure to caffeine on dopamine transmission: preclinical evidence and potential consequences of caffeine consumption

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Abstract: - Caffeine is a most popular psychostimulant and is consumed worldwide. A large body of evidence demonstrates the existence of striking differences between the effects of caffeine and those of psychostimulants bearing abuse potential, like amphetamines and cocaine, a major one being that the reinforcing properties of caffeine are generally modest. Nevertheless, preclinical research has suggested that caffeine, similar to addictive psychostimulants, is capable of interacting with dopaminergic circuits in the brain and, accordingly, of influencing dopamine-mediated neurobehavioural functions. Here evidence is derived from an experimental model of long-term caffeine administration in the rat which demonstrates that caffeine can exert an enduring facilitatory influence on dopamine transmission in the corpus striatum. Such an effect was found to be manifested as the development of sensitization to caffeine-induced motor stimulant effects, and as the onset of modifications involving receptors and immediate early gene expression in the striatum. Moreover, an increased responsiveness to the motor stimulation and striatal immediate early gene expression elicited by D-amphetamine was observed in rats pre-exposed to caffeine, further supporting the ability of caffeine to induce a hyperfunctionality of dopamine transmission. Taken together, these results lend support to the hypothesis that caffeine consumption might represent a factor capable of amplifying certain behaviours and/or pathologies (e.g., drug addiction, psychosis) which depend on a hyperactive dopamine transmission.

Key-Words: -animal models, behavioural sensitization, dopamine receptors, drug abuse, immediate early gene, psychosis, psychostimulants

1 Introduction
Caffeine is present in many beverages and foods like coffee, tea, soft drinks (as sodas and “energy drinks”) maté, candies and chocolate [1]. In the light of the widespread diffusion of these products, it is reasonable to assume that the general population, both young and adult, is constantly exposed to caffeine. Caffeine can exert a wide array of pharmacological effects and it can influence the function of several body organs including brain, heart, lungs and kidney [2]. However, the ability of caffeine to elicit psychostimulation is the effect which drives its widespread consumption [3]. The psychostimulant effects of caffeine include increase in wakefulness, delay in the need for sleep, elevation in alertness and attention. In addition, caffeine possesses rewarding properties and can act as a reinforcer, though under limited conditions [4]. The overall weakness of the reinforcing effects caffeine can exert is considered a major point of difference between caffeine and other widely consumed psychostimulants, either licit or illicit, such as amphetamines, cocaine and nicotine [5].

It is now well ascertained that caffeine elicits its psychostimulant effects by antagonizing the A1 and A2A adenosine receptors in the brain [3]. Exhaustive evidence in this sense has been obtained in experimental animals by means of studies involving both behavioural pharmacology and genetic approaches [6,7]. Further to demonstrating a major role for adenosine in caffeine-mediated psychostimulation, data collected by means of the same techniques also clearly show that dopamine transmission powerfully influences such an effect of caffeine [8,9]. The dependence of dopamine-induced psychostimulation on dopamine may be explained in the light of the profound opposite functional interactions existing between adenosine receptors and dopamine receptors, as shown by neuroanatomical and biochemical studies [10]. In this regard, it is worth mentioning that antagonism of adenosine receptors has been shown to amplify the effects mediated by the stimulation of dopamine receptors [11]. Therefore, blockade of adenosine receptors by caffeine provides a mechanism which directly links caffeine-induced psychostimulation to dopamine transmission. Of great interest is also the evidence showing that, next to depending on dopamine transmission for the elicitation of its effects, caffeine itself may impact the dopaminergic system [12]. On this basis, it can be hypothesized that caffeine consumption could interfere with dopamine-
dependent neurobehavioural functions such as, for example, emotional control and goal-directed behaviour [13,14]. Thus, interactions between caffeine and dopamine transmission have been envisioned as a mechanism which could underlie the joint consumption of caffeine and other psychoactive substances bearing abuse potential [3,12] as well as the manifestation of psychiatric-like symptoms which can be displayed, although very rarely, by caffeine consumers [15]. Although the study of caffeine-dopamine interactions has attracted a great deal of interest, to date conflicting results on this issue are reported in the literature [16,17,18]. This is due, in the first place, to the fact that caffeine can exert variable effects according to its doses and protocols of administration [3]. Moreover, many studies addressing this issue through a pharmacological approach do not adequately distinguish the possible additivity between caffeine and other substances targeting the dopaminergic system from the genuine modifications caffeine might induce in dopamine transmission.

2 Problem formulation
To develop a pharmacological paradigm to be used in experimental rodents for the study of the influence caffeine can exert on the function of dopamine transmission. The use of this paradigm should minimize all the variables which could complicate the interpretation of the results obtained in terms of caffeine-dopamine interactions.

3 Problem solution
Development of an experimental paradigm employing a subchronic-intermittent regimen of caffeine administration at a moderate dose (15 mg/kg, i.p., every other day for a total of 7 administrations) to male rats. This paradigm also utilizes a 3 days wash-out period between the last administration of caffeine and the evaluation of the possible modifications in dopamine transmission induced by caffeine. In the light of the fact that the plasmatic half-life of caffeine in the rat is of 0.7-1.2 h [3], the use of such an intermittent administration together with the wash-out period allows avoiding the presence of residual caffeine and of its metabolites, which could potentially influence the results observed. Therefore, this experimental paradigm is suited to the study of caffeine-dopamine interactions with little or no interference of pharmacological additivity [19].

To clarify whether prolonged exposure to caffeine was capable of triggering neuroadaptive modifications involving dopamine transmission, different behavioural and neurochemical parameters were examined by means of this paradigm [19,20,21,22]. In particular, the attention was focused on: a) development of sensitization to the motor stimulant effects of caffeine, b) evaluation of the influence of caffeine on the striatal levels of the immediate early gene zif-268, the expression of which is regulated by dopamine receptors, c) measurement of caffeine-stimulated dopamine release in the striatum, d) evaluation of the levels of adenosine A2A, dopamine D1 and D2 receptors and of the affinity state of D2 receptors in the striatum, e) evaluation of possible changes in motor stimulation, levels of zif-268 and dopamine release in the striatum after an acute administration of the dopaminomimetic psychostimulant D-amphetamine to rats previously exposed to caffeine (Fig. 1).

4 Conclusions
The results observed in rats exposed to subchronic-intermittent caffeine show that such a prolonged exposure to caffeine engenders: a) sensitization to the motor stimulant effects of caffeine itself, b) enduring amplification of the depressant effects of caffeine on the expression of the immediate early gene zif-268 in the striatum, c) persistent reduction in the striatal levels of A2A receptors and an increase in the portion of D2 receptors bearing high affinity for dopamine (D2 High), but not in the...
It is known that the development of sensitization to the motor stimulant effects of a psychoactive substance reflects, in part, the onset of facilitatory neuroplastic changes involving dopamine transmission [13]. Moreover, it is also ascertained that adenosine receptors and dopamine receptors interact in an opposite fashion at both the biochemical and behavioural level, where a reduction in adenosinergic tone results in a facilitation of dopamine transmission [11]. Therefore, the sensitized response to motor stimulation and zif-268 expression elicited by either caffeine or amphetamine, in the light of the crucial role played by striatal dopamine transmission in substance abuse [13]. It is worth mentioning that caffeine is often jointly consumed in social settings with substances as amphetamine analogs and alcohol [23,24], and that caffeine intake is often reported as a correlate in drug abuse [25,26].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle-pretreated rats</th>
<th>Caffeine-pretreated rats</th>
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<tbody>
<tr>
<td>motor activity stimulated by acute caffeine</td>
<td>+ 646% ± 12%</td>
<td>+ 1060% ± 15%</td>
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<tr>
<td>zif-268 expression stimulated by acute caffeine</td>
<td>- 25% ± 3%</td>
<td>- 47% ± 3%</td>
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<tr>
<td>motor activity stimulated by acute D-amphetamine</td>
<td>+ 567% ± 18%</td>
<td>+ 1415% ± 8%</td>
</tr>
<tr>
<td>zif-268 expression stimulated by acute D-amphetamine</td>
<td>+ 9% ± 1%</td>
<td>+ 20% ± 3%</td>
</tr>
<tr>
<td>dopamine release stimulated by acute D-amphetamine (peak)</td>
<td>+ 280% ± 30%</td>
<td>+ 295% ± 25%</td>
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<tr>
<td>levels of A2A receptors</td>
<td>± 0%</td>
<td>-25% ± 4%</td>
</tr>
<tr>
<td>levels of D1 receptors</td>
<td>± 0%</td>
<td>+3% ± 2%</td>
</tr>
<tr>
<td>levels of D2 receptors</td>
<td>± 0%</td>
<td>+2% ± 2%</td>
</tr>
<tr>
<td>proportion of D2 receptors bearing high affinity for dopamine</td>
<td>± 0%</td>
<td>+126% ± 6%</td>
</tr>
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It is often reported as a correlate in drug abuse [25,26]. Caffeine-induced hyperfunctionality of striatal dopamine transmission may also have relevance to neurobiological phenomena other than the interactions between caffeine and substances of abuse. Thus, the existence of dopaminergic hyperactivity has been suggested to underlie psychosis [29] and caffeine is capable of triggering the manifestation of psychotic-like symptoms, though in a very scarce number of caffeine consumers [15]. In line with this evidence, data observed in rats exposed to subchronic intermittent caffeine suggest that caffeine intake might potentially exacerbate psychosis, at least in those subjects who are prone to it. Influence of caffeine on dopamine transmission, however, could also have beneficial effects on other dopamine-dependent functions like attention and memory, as suggested by previous studies demonstrating an improvement of these functions by caffeine [30,31].

In summary, results observed in rats subjected to subchronic intermittent caffeine demonstrate that caffeine can elicit a hyperfunctional state of dopamine transmission in the striatum. Such a dopaminergic hyperfunctionality may have important implications for a wide array of neurobiological phenomena, ranging from drug abuse to emotional control, regulated by dopamine transmission.
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