

Effects of apomorphine on rat behavior in the elevated plus-maze

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Abstract

It has been reported that novelty may evoke both an exploratory and a fear drive, thus generating behavior responding to an approach/avoidance conflict. However, not much is known about the approach component. Whereas there exists abundant evidence referring to the avoidance component as the main target for the anxiolytic action of benzodiazepines, the involvement of dopaminergic mechanisms in fear and anxiety is controversial. The present study examined the effects of the dopaminergic agonist apomorphine, the D₂ dopaminergic antagonist sulpiride and the combined treatment sulpiride plus apomorphine on conventional and non-conventional measures of the behavior of rats exposed to an elevated plus-maze. Systemic injection of apomorphine (0.25, 0.5 and 1.0 mg/kg) caused a selective increase in the time spent in the open arms and in the open arm extremities. Pre-treatment with sulpiride blocked these effects while this dopaminergic antagonist had no effect by its own. Apomorphine produced no significant effects on stretching, flat-back-approach or scanning. Therefore, apomorphine increased the behavioral response linked to the approach component of the conflict without affecting risk assessment behaviors. These findings suggest that dopaminergic mechanisms, probably through D₂ receptors, may also be involved in the mediation of the conflict derived from the need of gathering information for confirming, identifying and localizing danger and take the appropriate action for avoiding the threatening stimuli of the elevated plus-maze. A role for dopaminergic mechanisms in the setting up of adaptive responses in a fear-inducing environment is discussed.

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1. Introduction

The elevated plus-maze test has been used to study the multiple consequences elicited by the approach/avoidance conflict engendered by a number of stressful situations, such as the switch-off procedure, inhibitory avoidance, or two-way avoidance [20,26,28,33,38,40,42,44]. The analysis of the behavioral, autonomic and endocrine correlates of the defense reaction that results from the exposure of the animal to the height and openness of the elevated plus maze has contributed decisively to the neurobiology of anxiety. In general, the percent preference for open or closed arms, both for entries and time spent in them is taken as an index of anxiety: the more intense anxiety

the lower the percent preference for the open arms [27,39]. Increase or reduction caused by a given compound in the number of entries and time spent into the open arms have been taken as good indices of its anxiolytic or anxiogenic actions, respectively [38,39]. The test became more sensitive to detect anxiolytic and anxiogenic properties of drugs with the inclusion of the novel so-called ethological measures, such as head-dipping, end-arm exploration, stretching, rearing and others [11,13,14,45].

Much older than the elevated plus-maze, the open-field was one of the most popular procedures in animal psychology [for a review, see Ref. 41] and the literature is rich in reports showing increased locomotor activity with dopaminergic agonists [29,37,40]. Recently, we have shown a steady increase in exploratory behavior by rats given apomorphine and submitted to an open-field test [21].

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Whereas serotonergic, neuropeptide, GABAergic and several other mechanisms have long been shown to be implicated in the modulation of fear and anxiety, dopaminergic mechanisms have been related to the production and elaboration of acute and chronic stress (for example, see Refs. [10,44]). Indeed, current knowledge indicates that cortical dopamine projections are activated by a wide variety of aversive stimulation [1,18,22]. In this context, it has been shown that acute environmental stressors release dopamine from the cortical dopaminergic terminals [3,7,18,19]. Recent reports have begun to associate these mechanisms with fear-like behavior in mesencephalic structures. Indeed, it has been shown that the aversive stimulation of structures belonging to the so-called brain aversion system (such as the dorsal periaqueductal gray matter and the inferior colliculi) enhances dopamine release in the prefrontal cortex [16]. Support for the notion that dopamine release is associated to the aversive properties of stimuli comes from the fact that such a release is inhibited by diazepam [19].

The above-mentioned findings could be taken as evidence for a secondary involvement of dopamine in fear-like states elicited by acute aversive stimuli but do not add much to our knowledge on the kind of defensive responses associated with the dopaminergic mechanisms. Traditionally, dopaminergic mechanisms of the mesolimbic/mesocortical systems have been associated to the heightened motivation to explore and approach environmental stimuli [1,12,29]. In addition, in spite of the variety of animal models of anxiety there is some uncertainty as to whether anxiety mechanisms and anxiolytic drugs are uniformly active when using a particular test or comparing different tests [26]. It seems that, depending on the test, some degree of conflict is responsible for the defensive behaviors animals express when facing threatening situations. For example, many of the behavioral categories measured in the elevated plus-maze are the result of a conflict generated by the activation of an approach/avoidance system [24,33,46]. While, serotonergic and GABA/BZD agents seem to produce their anxiolytic effects by reducing the avoidance component, little is known about the mechanisms responsible for the approach component of this system. This latter aspect gains importance insofar as increased exploratory activity in the elevated plus-maze may be attributed to reduction of the avoidance component, increased approach in such a conflict paradigm or even heightened motor activity or enhanced drive to explore.

Apomorphine is a dopaminergic agonist with unique properties which, differently from other agents of this class of compounds, has been used for some clinic purposes, such as erectile dysfunction and Parkinson disease [2,6]. Although the effects of apomorphine on stressful conditions has been studied with several laboratory tests [21,29,50] little is known on its effects in the elevated plus-maze, an

animal model of anxiety based on the conflict that results from the natural tendency of the animals to approach and avoid dangerous situations [24]. For this reason, this study was undertaken to examine the effects of apomorphine in the elevated plus-maze. Since apomorphine has been considered a nonselective dopaminergic agonist [12,31], we challenge the effects of this dopaminergic agonist with sulpiride, considered to be a D₂ selective antagonist [25,29,49,51].

2. Method

2.1. Animals

Male Wistar-derived rats from the animal house of the University of São Paulo at Ribeirão Preto were used as subjects. The animals weighed 230–250 g and were housed in polypropylene cages (40 × 34 × 17 cm) in groups of six under a 12:12 dark/light cycle (lights on at 07:00 hours) and a temperature kept at 24 ± 1 °C, with free access to food and water throughout the experiment. All the subjects were naïve and submitted to a habituation period of 3 days before the beginning of the experiment. The experiments reported in this paper were performed in compliance with the recommendations of the Brazilian Society of Neuroscience and Behavior which, in turn, are based on the US National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Apparatus

An elevated plus-maze, as described in detail elsewhere [30] was used. It consisted of two open arms (50 × 10 cm) crossed at right angles with two opposed arms of the same size. Two of the opposed arms were enclosed by walls 40 cm high, except for the central part where the arms crossed. The whole apparatus was elevated 50 cm above the floor. To prevent the rats from falling, a rim of Plexiglas (0.5 cm high) surrounded the perimeter of the open arms. The experimental sessions were recorded by video camera interfaced with a monitor and a VCR in an adjacent room. In order to record displacements and other behaviors, the image of the elevated plus-maze was divided into 10-cm squares in a transparent mask placed on the TV screen. This allowed the recording of the number of squares entered by the animal as well as the exact place of occurrence of recorded behaviors.

2.3. Procedure

The rats were studied in three groups according to the drug and dose injected: apomorphine (saline, 0.25, 0.5 and 1.0 mg/kg, *N*=12, 9, 13 and 10, respectively), sulpiride (saline, 10, 20 and 40 mg/kg, *N*=8, 7, 8 and 8, respectively) and antagonism (saline, 0.5 mg/kg apomorphine and 40 mg/

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