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Role of learning of open arm avoidance in the phenomenon of one-trial tolerance to the anxiolytic effect of chlordiazepoxide in mice

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Abstract

A single exposure to the elevated plus-maze (EPM) test of anxiety reduces or abolishes the anxiolytic efficacy of benzodiazepines on a second trial. Some possible explanations to the occurrence of this phenomenon (one-trial tolerance-OTT) involve behavioral modifications thought to be consequence of some kind of learning in the first trial. In the present study, the influence of learning-impairing situations on the effects of the benzodiazepine chlordiazepoxide on mice re-tested in the EPM is investigated. The results showed that: (1) as expected, the administration of chlordiazepoxide to mice re-tested in the EPM- under the same conditions of the first trial- failed to induce anxiolysis; (2) a decreased percent time in the open arms was observed on the second trial of mice exposed to both trials under the same experimental conditions; (3) neither the increase in open arm avoidance by mice re-exposed to the EPM nor the OTT to chlordiazepoxide effect were modified by administration of the amnestic agent scopolamine; (4) the decrement of the duration of the first trial to 1 min or the change in light and noise conditions in both trials counteracted the increase in open arm avoidance on trial 2; (5) none of the later procedures modified the phenomenon of OTT. Although

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not discarding the modulation exerted by other memory processes in the OTT phenomenon, the results indicate that situations that impair the learned avoidance response to the open arms in the EPM do not modify the phenomenon of OTT.

Keywords: Chlordiazepoxide; Elevated plus-maze; Tolerance; Anxiety; Learning

Introduction

Although the elevated plus-maze (EPM) has been used to evaluate memory (Silva et al., 1997; Silva and Frussa-Filho, 2000) and to induce anxiety (Rodgers et al., 1992; Conceição et al., 1992), doubtless it has been most extensively used to assess the anxiolytic and anxiogenic effects of drugs. Indeed, it is the most widely used of all currently available animal models of anxiety that depend upon the use of spontaneous behavior (Rodgers et al., 1996). However, in spite of the widespread appeal, the EPM model has an intriguing feature: the phenomenon of "one-trial tolerance" (OTT). There is a marked attenuation or even abolition of the anxiolytic effect of benzodiazepines in rats and mice by a single previous experience of the maze (File et al., 1990; Rodgers et al., 1992; File et al., 1993; Rodgers and Shepherd, 1993; Gonzalez and File, 1997; Frussa-Filho et al., 1999; Pereira et al., 1999; Frussa-Filho et al., 2002). The phenomenon of OTT is not dependent on the drug treatment on trial 1, as well as on the material from which the maze is constructed (File et al., 1990). It has been reported to occur with inter-test intervals ranging from 24 hours to 2 weeks (File et al., 1990; Rodgers et al., 1992; Rodgers and Shepherd, 1993). Furthermore, increasing the duration of trial 1 to 10 minutes does not modify the lack of benzodiazepine efficacy on a 5-minute duration re-exposure (Holmes and Rodgers, 1999).

As pointed out by Gonzalez and File (1997), no conclusive explanation has been found for this phenomenon, but several hypotheses have been suggested. First of all, the phenomenon of OTT has been suggested to represent the acquisition of a phobic-like response to the open arms during trial 1, with the absence of benzodiazepines anxiolysis on trial 2, which may agree with the lack of effect of these drugs in phobia (File et al., 1993; File and Zagrossi, 1993). Alternatively, Rodgers and Shepherd (1993) suggested that the loss of diazepam efficacy on trial 2 might reflect a relative absence of an approach/avoid conflict. In other words, prior knowledge of the maze would reduce the tendency to explore these natural aversive areas, thereby reducing conflict and eliminating a possible response to diazepam. This hypothesis was corroborated by the observation that the phenomenon of OTT is abolished by the introduction of a motivational conflict situation during trial 2 (Pereira et al., 1999). Finally, Dawson et al. (1994) have suggested that the lost of efficacy of benzodiazepines on trial 2 could be a result of habituation of exploratory behavior. Accordingly, rodents previously exposed to the EPM show decreased open arm time on re-exposure (Rodgers et al., 1992, 1996; Lee and Rodgers, 1990; Almeida et al., 1993; Griebel et al., 1993; Treit et al., 1993; Rodgers and Shepherd, 1993; Dawson et al., 1994), indicating that there is some kind of learning involved in open arms avoidance (File et al., 1990). In this respect, Rodgers et al. (1996) suggested that the retrieval of this learning would result in a different behavioral response upon second exposure, irrespective to the drug treatment.