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Age differences in an animal model of obsessive–compulsive disorder: participation of dopamine
Dopamine in an animal model of OCD

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Abstract

The putative age difference in the effect of chronically administered quinpirole (0.125 and 0.5 mg/kg, 11 injections) on alternation in a T maze was studied. Male juvenile (43 days old) and adult (around 90 days old) rats exhibited similar control values of alternation. In adults, quinpirole (0.5 mg/kg) produced a drastic perseveration after 10 and 11 injections (mean number of repetitive choices of 3.4 and 3.1, respectively); conversely, in juvenile, such treatment produced a less marked perseveration (mean number of repetitive choices of 1.7 and 2.1, for the 10th and 11th injection, respectively). We also studied the age difference in the protective actions of clomipramine subchronically administered (15 mg/kg, three times) on the quinpirole-induced perseveration. Clearly, as previously demonstrated, in adult animals, this tricyclic antidepressant completely prevented the drug-induced perseveration (mean number of repetitive choices of 1.7); while in juvenile, animals only produced a weak action (mean number of repetitive choices of 1.8). Data agreed with basic research showing a hyposensitivity of juvenile animals to dopaminergic agonists and with clinical findings suggesting a weaker effect of clomipramine treatment in youth. These results reinforce perseveration in a T maze as a useful animal model for studying age differences in obsessive–compulsive disorder (OCD).

Keywords: Age differences; Quinpirole-induced perseveration; T maze; Clomipramine; Obsessive–compulsive disorder; Animal model

1. Introduction

The research on obsessive–compulsive disorder (OCD) using animal models has exploited the expression of natural or pharmacologically induced repetitive behaviors in various species (Stein, 2000; Szechtman et al., 1998; Woods et al., 1993; Yadin et al., 1991). Indeed, the administration of serotonin and dopamine agonists has shown to produce perseverative responses (Seibell et al., 2003; Szechtman et al., 1998; Whitaker-Azmitia et al., 1990; Yadin et al., 1991). Yadin et al. (1991) demonstrated that the administration of 5-HT agonists produces a disruption of spontaneous alteration, defined as the natural tendency exhibited by rodents to first enter one and then the other alley of a T maze in two successive, equally rewarded trials (Ellen and Deloache, 1968). Such disruption is manifested as perseverative choices of the same arm (Seibell et al., 2003; Szechtman et al., 1998; Whitaker-Azmitia et al., 1990; Yadin et al., 1991).

The perseverative actions observed after chronic administration of quinpirole, an agonist of D_2/D_3 receptors, have been described in different animal models. Initially and most importantly for the present study, Einat and Szechtman (1995) reported that quinpirole induces perseverative behavior in a T maze. In this test, animals exhibited reduced alternation when compared to controls. Moreover, Szechtman et al. (1998) demonstrated that this treatment produced compulsive checking. These data suggest that the chronic administration of quinpirole constitutes a useful tool in animal models of OCD.

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A number of studies have shown that dopaminergic behaviors are attenuated or reversed by increasing the serotonergic transmission (Whitaker-Azmitia et al., 1990). Indeed, the perseverative actions of quinpirole and other dopaminergic agonists can be effectively prevented by the administration of clomipramine (Szechtman et al., 1998; Whitaker-Azmitia et al., 1990), the most extensively studied drug for the treatment of OCD (DeVaugh-Geiss, 1991; Leonard et al., 1989; Pigott and Seay, 1999). This finding exposes the interaction between dopamine and serotonin in the control of experimentally induced compulsions and in the neurochemistry of the human disorder (Austin et al., 1991; Greist et al., 1995; Wise and Rapoport, 1989).

It is worth mentioning that most of these results have been obtained in adult male rats, with little or no attention to other age periods. The period from Postnatal Days 30–50 is defined as "periadolescence" in rats. This developmental stage has been poorly studied despite striking differences in behavior, physiology, and neurotransmission (Spear and Brake, 1983). On these bases, we recently reported age differences in the perseverative actions of the serotonergic agonist 8-hydroxy-2-di-*n*-(propylamino)-tetralin (8-OH-DPAT) and in the protective effect of clomipramine. We found that male periadolescent rats were more sensitive to the perseveration induced by 8-OH-DPAT but less responsive to clomipramine than adults were (Fernández-Guasti et al., 2003). These results resemble the human OCD features, where the response to treatment with selective serotonin reuptake inhibitors (SSRIs) is weaker in children than in their adult counterparts (Geller et al., 1998; 2001).

The purpose of the present study was to compare possible age differences in the perseverative actions of chronic treatment with quinpirole and in the preventive action of clomipramine. In these experiments, the perseveration in a T maze was used as an animal model of compulsive behavior.

2. Materials and methods

2.1. Animals

Sixty male Wistar rats from different litters bred in this laboratory were used in this study. Juvenile animals were aged 21 days at the start of the injection regimen and 43 days at the end of the tests. Adult animals were about 90 days of age and weighed around 340 g at the end of the drug treatment. All animals were kept in a room under inverted 12:12-h light–dark cycle conditions (light on at 22:00 h) at least 10 days before the beginning of the experiments. Animals were housed eight per cage. Behavioral tests were performed between 11:00 and 16:00 h. The Local Committee of Ethics on Animal Experimentation approved all experimental procedures, which followed the regulations established in the Mexican official norm for the use and care of laboratory animals "NOM-062-ZOO-1999".

2.2. Apparatus

The testing apparatus for spontaneous alternation was a Plexiglas T maze with goal boxes characterized by distinctive cues (Seibell et al., 2003; Yadin et al., 1991). All arms (including the main arm and the two goal boxes) measured 50×10 cm. Guillotine doors separated the main arm and the goal boxes from the main body of the maze. Small plastic cups were placed at the corners of both goal boxes. The maze was covered with clear Plexiglas lids. The maze was cleaned after each animal test.

2.3. Drugs

The D_2/D_3 agonist, quinpirole HCl (RBI, St. Louis, MO, USA) was dissolved in saline in a volume of 2 ml/kg and injected to rats at 0.125 or 0.5 mg/kg ip doses on alternating days. The tricyclic antidepressant, clomipramine (CMI, Sigma, St. Louis, MO, USA) was dissolved in saline and injected at 15 mg/kg sc in 2 ml at 24, 4, and 1 h before the last injection of quinpirole. This subchronic treatment has been demonstrated to be effective in preventing the perseveration induced by the administration of a serotonergic agonist in an animal model of OCD (Fernández-Guasti et al., 2003). The same scheme of quinpirole and CMI was used in juvenile and adult animals.

2.4. Procedure

The experiments were conducted throughout 22 days, during which animals received 11 injections of quinpirole. The first six injections (Days 1 to 12) were administered to the animals in their home cages with no training on the T maze. On the 14th day, the animals were habituated to the T maze for 20 min, during which they were allowed to explore the entire area and were exposed to chocolate milk in their home cages to acquaint them with the novel stimulus. On the 15th day, animals were confined for 5 min in each goal arm where chocolate milk was available.

On the 16th day, animals were placed in the main arm; the guillotine doors were lifted, and rats were allowed to choose between the two goal arms, both of which were baited with chocolate milk. When the rat placed all four paws in one of the goal boxes and approached the milk cup (animals were allowed to drink the chocolate milk), it was considered as a choice. Thereafter, the rats were removed and were placed in a holding cage for 10 s. This procedure was repeated for a total of nine runs followed by the application of the 8th quinpirole injection. Inasmuch as previous reports showed a lack of perseverative effect of quinpirole before the 8th injection (Einat and Szechtman, 1995), the performance on this day was considered as the basal control value.

The last two injections (10th and 11th), corresponding to the experimental tests, were preceded by a training session, in which animals were tested as many times as needed until

they alternated their choice up to seven runs. They were injected with quinpirole and tested again 1 h later (Einat and Szechtman, 1995). Throughout the experiment, the animals that did not complete the test were excluded; therefore, based on their performance after the injections, a given animal could be considered a proficient alternator or a perseverator as follows:

Proficient alternators: These animals first entered one and then the other arm in two successive trials. They were assigned 1 as their number of repetitive choices.
Perseverators: These animals chose the same arm in two or more consecutive trials. Their number of repetitive choices of the same arm could vary between 2 and 7. For example, if a given animal chose the right arm in four consecutive trials before going to the left arm, its number of repetitive choices was 4.

As previously reported (Richman et al., 1986/1987, Yadin et al., 1991), the most important variable proposed to indicate compulsive behavior was the number of repetitive choices or perseverative responses (the same goal arm choices) until an alternation occurred. The data are expressed as group means ± S.E. Two main groups of animals were used: juvenile and adults. All animals received 10 quinpirole injections similarly. After this injection, the groups were divided into two subgroups, with all of them receiving an 11th injection of quinpirole but with half treated with saline (2.0 ml/kg) and the other half with clomipramine at 15 mg/kg three times. On these bases, the quinpirole treatment was considered as a dependent experiment, while the comparisons between the quinpirole plus saline and the quinpirole plus CMI was made between independent groups of rats.

2.5. Statistics

To compare putative age differences in the action of quinpirole, a two-way repeated-measures ANOVA, considering age, quinpirole treatment, and age by treatment interaction, was employed. A post hoc Tukey t test was used with a level of significance of $P<.05$. Specific group comparisons were made using the Student's t test. Finally, the percentage of change between the quinpirole plus saline and quinpirole plus CMI groups between both age groups was compared using the Fisher's Exact Test.

3. Results

The dose of 0.125 mg/kg of quinpirole did not produce perseverative effects in juvenile or in adult animals. Fig. 1 shows the alternation in a T maze of juvenile and adult male rats after 8 to 11 injections of quinpirole (0.5 mg/kg) and the protective actions of clomipramine. The two-way repeated-measures ANOVA for quinpirole treatment revealed significant differences for age [$F(1,102)=12.941$, $P=.001$], treatment [$F(2,101)=14.878$, $P<.001$], and the interaction between these factors [$F(2,101)=4.996$, $P=.04$]. As previously stated, the control basal value was established considering the alternation showed by the same animals after seven quinpirole injections at a dose of 0.5 mg/kg. Control juvenile and adult animals displayed similar levels of spontaneous alternation, such levels being close to 1 in both age groups. After 10 and 11 injections, clear age differences were observed for the perseverative actions of quinpirole. Thus, after 10 or 11 injections, juvenile animals showed a mild increase in perseveration, while adult animals displayed a drastic statistical significant perseveration. This figure also shows the age difference in the preventive action of clomipramine (15 mg/kg, three times) on the quinpirole-induced perseveration. Thus, in the adult animals, clomipramine completely reversed the perseveration induced by quinpirole; while in juvenile rats, treatment with clomipramine produced a weak effect. In addition, a statistically significant age difference was found in the percentage (Fisher's F test, $P<.05$) of reduced perseveration after CMI. In juvenile

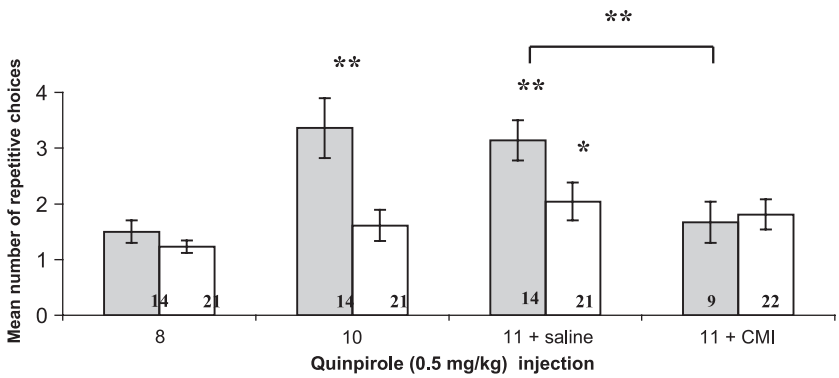

Fig. 1. Effect of the sequential administrations of quinpirole and CMI on alternation in a T maze in adult (solid bars) and juvenile rats (open bars). Bars represent the mean ± S.E. number of repetitive choices per group. Asterisks over bars represent comparison versus the basal control group (8th injection; Tukey t test, $*P<.05$, $**P<.01$). Asterisks over bracket represent comparison between the 11th quinpirole injection plus saline and the 11th quinpirole injection plus clomipramine groups (Student t, $**P<.01$). Each group's n is represented at the bottom part of the corresponding bar.

rats, such reduction was of 23% as compared with 69% in adult subjects.

4. Discussion

The present series of results show that, in an experimental paradigm of OCD, juvenile male rats are less sensitive to the perseverative actions of quinpirole than adult animals are and that clomipramine effectively prevents the drug-induced perseveration in adult animals, while in juvenile rats, it produces a weak effect.

Although serotonin seems to importantly mediate perseveration in this animal model (Fernández-Guasti et al., 2003; Seibell et al., 2003; Yadin et al., 1991), present and other reports indicate that the administration of dopaminergic agonists also produces perseverative behaviors (Bruto and Anisman, 1983; Einat and Szechtman, 1995; Molino et al., 1989; Szechtman et al., 1998; Van Hartesveldt, 1997). These data strengthen the idea that the dopaminergic transmission controls repetitive behaviors (Szechtman et al., 1998) and also plays a role in OCD (Goodman et al., 1990; Szechtman et al., 1999).

The mechanisms causing quinpirole disruption of spontaneous alternation are poorly understood (Szechtman et al., 1994, 1998; Van Hartesveldt, 1997). This phenomenon is possibly a result of a D_2 sensitization, which is implicated in the development of several psychopathologies (Szumlinski et al., 1997).The face validity of the sensitization model is strengthened by the fact that, as a result of repeated quinpirole administrations, new behaviors emerge, indicating an altered cognitive organization (Szechtman et al., 1994).

The possible explanations for such alternation include a decreased attractiveness of novelty, an enhanced appeal of familiar stimuli, and a diminution in the sense of task completion. This last possibility acquires importance in the context of the proposal that spontaneous alternation in a T maze may be an animal model of OCD (Einat and Szechtman, 1995; Fernández-Guasti et al., 2003; Seibell et al., 2003; Yadin et al., 1991). Specifically, the fact that the rat returns to the same arm of the maze may be interpreted as compulsive checking, in homology to that exhibited by OCD patients (Biederman et al., 1996; Geller et al., 2001; Hanna, 1995; Nicolini et al., 1997). It has been established that dopamine plays an important role in reinforcement and the participation of reinforcement in the pathogenesis of compulsive behavior (Pitman, 1989). According to the salience hypothesis, this neurotransmitter plays a central role in the conversion of a neural representation of any stimuli to an attractive or aversive entity (motivational salience) and provides an interface for the conversion of motivation into action (Berridge and Robinson, 1998; Kapur, 2003). In this way, the sense of lack of completion of a task in these animals and the urgency to perform a compulsion in the patients with OCD could be mediated, at least partially, by an enhanced dopaminergic transmission. The hippocampus seems to be the brain structure that mediates the "sense of completion" (Pitman, 1989) and participates in spontaneous alternation (Ellen and Deloache, 1968; Kokkinidis and Anisman, 1976). Furthermore, Einat and Szechtman (1995) proposed that quinpirole produces its perseverative action by acting at the hippocampus.

In the present study, we found that juvenile male rats were less sensitive to the perseverative actions of quinpirole (0.5 mg/kg). These data are in full agreement with some studies indicating that juvenile rats are unique with regard to psychopharmacological responses such as a particular hyposensitivity to the behavioral effects of dopamine agonists (Bolanos et al., 1998; Laviola et al., 1995; Spear and Brake, 1983).

The reasons explaining the age differential effect of quinpirole on perseveration could be of pharmacokinetic or pharmacodynamic nature. Regarding the former, no studies on the pharmacokinetics of quinpirole along development have been made, but it is possible that the dose of quinpirole used in the juvenile was insufficient to produce the same perseverative actions than in adults. This possibility appears unlikely, inasmuch as many behavioral alterations have been observed in response to a wide range of quinpirole doses even in younger animals (Moody and Spear, 1992; Moody et al., 1992). In relation with pharmacodynamic explanations, it has been established that dopamine D_2 receptors are detectable at birth (Sales et al., 1989) and increase their number until postnatal day 21, when adult levels of both number and binding are reached (Hartley and Seeman, 1983). Additionally, Wang and Pitts (1995) reported that the functional features of the D_2/D_3 receptors are already established in rats from 1 week of age. These data would not explain the age differences found for the perseverative actions of quinpirole. Another possible interpretation relies on the differential timing in the maturity of the serotonergic (Li et al., 2002), glutamatergic (Balla et al., 2003; Takahata and Moghaddam, 1998), and noradrenergic (Ventura et al., 2003) systems that modulate the dopaminergic transmission, modifying the behavioral responses between juvenile and adult rats.

The present results showed that clomipramine completely blocked the perseverative actions of quinpirole in adult animals. These data agree with previous reports demonstrating that clomipramine completely reversed the perseverative actions of the D_1 agonist SKF38393 (Whitaker-Azmitia et al., 1990) and importantly attenuated the quinpirole-induced compulsive checking (Szechtman et al., 1998). The reversal of CMI on quinpirole-induced perseveration could involve the drug effects on dopamine and serotonin release (Shiloh et al., 2000).

Present results also showed that CMI completely blocked the perseverative actions of quinpirole in adult males, while this same treatment only partially attenuated the perseveration of this dopamine agonist in juvenile rats. These data

agree with previous results (Fernández-Guasti et al., 2003) and clinical findings and suggest that juvenile rats (and possibly humans) displayed perseveration and a type of OCD less responsive to clomipramine (Leonard et al., 1989; Pigott and Seay, 1999). It could be argued that the weak clomipramine action in immature animals is veiled by a "floor effect" due to the consistently low response to quinpirole in this age group. Although this interpretation cannot be completely disregarded, the present finding showing that, in juvenile rats, the percentage of perseverative reduction after clomipramine treatment was 23% (as compared with 69% in their adult counterpart) disagrees with this idea. The weaker effect of clomipramine in juvenile animals can be explained on the bases of three nonexclusive interpretations: first, a lack of maturation of the serotonergic control over the dopaminergic system (vide supra) (Bero and Kuhn, 1987; Moguilevski et al., 1990); second, a lower brain disposition of CMI in juvenile rats due to pharmacokinetic factors; and third, a lower sensitivity in the serotonin transporter (5-HTT). In favor of this last hypothesis is the age of onset of OCD (independently of the duration of illness) as a predictor of response to treatment (Rosario-Campos et al., 2001). In further support of age differences in the sensitivity of the 5-HTT, studies performed in children and adults with OCD have shown that the administration of similar or even higher doses of clomipramine results in a lower percentage of improvement in children (Leonard et al., 1989).

In closing, it should be mentioned that an important reason to investigate psychopharmacology in periadolescent subjects is to develop age-appropriate pharmacological treatments for psychiatric disorders. This is especially important in the current era of increased diagnosis of anxiety, depression, psychosis, and OCD in youth (Cassidy and Jellinek, 1998; Fombonne, 1998).

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