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Ontogenetic quinpirole treatments produce spatial memory deficits and enhance skilled reaching in adult rats

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Abstract

There is a paucity of data on neurochemical abnormalities and associated effects on cognition and motor performance in rats ontogenetically treated with quinpirole, a rodent model of dopaminergic hyperfunction. The objective of the current study was to analyze the cognitive and motor effects produced by ontogenetic administration of quinpirole, a dopamine D_2/D_3 receptor agonist. Past research from this laboratory has shown that ontogenetic quinpirole treatment sensitizes D_2 receptors and produces a variety of characteristic stereotypic behaviors in adult rats. In the current study, rats received quinpirole HCl (1 mg/kg/day) or saline from postnatal day (PD) 1 to PD 11 and went otherwise untreated until adulthood (PD 60). In Experiment 1, cognitive performance was assessed on the standard and matching-to-place versions of the Morris water task (MWT). In Experiment 2, skilled motor performance was assessed on the Whishaw reaching task and locomotor activity was also analyzed. We found that ontogenetically quinpirole-treated rats displayed a deficit on the probe trial given at the end of training of the standard version of the MWT but that there were no significant differences from control on the matching-to-place task. Additionally, rats treated in ontogeny with quinpirole showed significant enhancement in reaching accuracy on the Whishaw reaching task as well as increased locomotor activity relative to saline controls. These findings demonstrate that ontogenetic quinpirole treatments produce cognitive deficits, enhanced skilled reaching and hyperlocomotion. The behavioral changes produced by ontogenetic quinpirole treatment are consistent with dopaminergic hyperfunction, and possible mechanisms are discussed.

Keywords: Development; Quinpirole; Morris water task; Whishaw reaching task; Cognitive deficits; Skilled reaching

1. Introduction

Dopaminergic dysfunction has been implicated in a number of neurological and neuropsychiatric disorders, including schizophrenia, obsessive-compulsive disorder (OCD) and Tourette's syndrome (Blum et al., 2000; Depatie and Lal, 2001; Finlay, 2001; Goodman and Pardee, 2000; Hannesson and Skelton, 1998; Kokkinidis and Anisman, 1980; Mackay et al., 1982; Purcell et al., 1998; Ramasubba et al., 2000; Schmidtke et al., 1998). Patients suffering from these disorders exhibit an exceedingly broad behavioral syndrome that includes abnormal ideation, altered perception, thought disorder, motor dysfunction, repetitive checking behavior and explosive verbal outbursts (Budman et al., 1998; Como, 2001; Spitzer, 1997; Wilson et al., 1998). It has been discovered that patients suffering from these disorders demonstrate increased dopaminergic function that includes long-term changes in sensitivity and density of dopaminergic receptors and changes in dopaminergic release (Blum et al., 2000; Harvey et al., 2001; Schmidtke et al., 1998; Spitzer, 1997). A recent research focus has been on the cognitive deficits produced by disorders associated with dopaminergic hyperfunction. For example, schizophrenics exhibit impairments on tasks requiring selective attention, long-term memory or action planning (Elvevag and Goldberg, 2000; Kuperberg and Heckers, 2000; Lussier and Stip, 2001; Thaker and Carpenter, 2001). Likewise, cognitive deficits have also been observed in patients suffering from OCD and Tourette's syndrome on a variety of behavioral tasks (Blum et al., 2000; Como, 2001; Zitterl et al., 2001). However, there has been little information associating sensitivity changes in the dopaminergic D2 receptor produced by ontogenetic treatments and cognitive and motor function.

Cognitive deficits have been observed in rodent models of mental disorders associated with increased dopamine func-

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tion. In a rodent model of schizophrenia, rats are given neonatal ventral hippocampal lesions or frontal cortex lesions in adulthood. A variety of cognitive deficits and social behavioral deficits have been observed, including spatial memory deficits on the radial arm maze, Morris water task (MWT) and discrimination tasks (Chambers et al., 1996; Hanlon and Sutherland, 2000; Joel and Weiner, 2000; Joel et al., 1997; Maes et al., 2001; Sams-Dodd et al., 1997). The focus of these rodent models utilizing brain lesions is not only to model the pathophysiology in the frontal cortex and hippocampus that is observed in human schizophrenics but also to model some of the behavioral deficits due to cognitive dysfunction. Likewise, patients suffering from OCD also demonstrate pathophysiology in the frontal cortex and demonstrate specific cognitive deficits on tasks of executive and visual memory function (Schmidtke et al., 1998) and controlled attentional processing (Zitterl et al., 2001). A "neurochemical" rodent model has also been utilized to replicate increased dopamine function, produced by chronic amphetamine treatment (Kokkinidis and Anisman, 1980). Amphetamine produces robust release of dopamine in the nucleus accumbens, striatum and frontal cortex (Groves and Rebec, 1976; Kokkinidis and Anisman, 1980). Additionally, other models of animal psychosis have utilized cocaine, a drug that increases dopaminergic function, produces degeneration in the lateral habenula and fasciculus retroflexus and causes cognitive deficits when ontogenetically administered (Inman-Wood et al., 2000; Murphy et al., 1999; Ellison et al., 1996). However, it is well known that dopaminergic dysfunction is but one of the many neurochemical abnormalities in schizophrenia, OCD and other mental disorders (Arranz et al., 2001; Camarena et al., 2001; Schmidtke et al., 1998). Conversely, dysfunction in the dopaminergic system produces changes in other neurochemical systems, which may play an important role in some of the behavioral abnormalities observed in these disorders (Szechtman et al., 2001; Tizabi et al., 1999). Therefore, it appears that increases in dopaminergic functioning may result in cognitive deficits, but the specific neurobiological mechanism has not been elucidated.

Increases in dopaminergic function are generally associated with improvements in skilled motor performance. It is well known that Parkinson's disease produces degeneration of dopaminergic neurons, which results in a decreased ability to perform skilled reaching tasks (Olsson et al., 1995). Past research has shown that quinpirole aids in recovery of skilled motor function after striatal lesions and that D_2 receptor activation enhances skilled motor performance (Fricker et al., 1997). Based on past results by Kostrzewa et al. (Kostrzewa and Brus, 1991; Kostrzewa et al., 1990, 1993a,b) that have shown ontogenetic quinpirole treatments produce supersensitization of the D_2 receptor, it would seem to follow that increased dopaminergic function should generally result in an enhancement of skilled motor behaviors.

Chronic ontogenetic treatment of rat pups with quinpirole, an agonist at D_2/D_3 dopamine receptors, produces enhanced quinpirole-induced behaviors in adulthood: hyperlocomotor activity, increased yawning, paw treading and vertical jumping, which are effects apparently related to D_2 receptor supersensitization (Kostrzewa and Brus, 1991; Kostrzewa et al., 1990, 1993a,b). All of these behavioral changes can be reversed by the neuroleptic haloperidol, a D_2 receptor blocker, suggesting that this rodent model may be suitable for screening the efficacy of putative neuroleptics. Additionally in this model, nicotine was found to antagonize quinpirole-induced hyperlocomotor activity, suggesting its therapeutic potential (Tizabi et al., 1999). This finding is congruent with earlier findings by Freedman et al. that have shown that individuals suffering from psychological disorders associated with dopamine hyperfunction that smoke may utilize nicotine to alleviate some of the sensory gating and stereotypic behavior caused by the disorder (Adler et al., 1998; Griffith et al., 1998; Leonard et al., 2000).

In the current study, we assessed the effects of ontogenetic quinpirole treatments on cognitive and motor function in rats. Female Sprague–Dawley rats were treated from postnatal day (PD) 1 to PD 11 with quinpirole HCl (1 mg/kg) then tested as adults (starting at PD 60) on the MWT (Experiment 1) and Whishaw reaching task and locomotor activity (Experiment 2) to analyze cognitive and motor function, respectively. In prior studies, dopaminergic dysfunction has been found to produce a deficit on cognitively complex behavioral tasks such as the MWT (Archer et al., 1998; Eiant and Szechtman, 1993). In addition, generally, drugs that enhance dopaminergic function have been associated with enhanced performance on skilled motor tasks (Fricker et al., 1997). Additionally, in previous studies, male rats have been prevalently utilized, and in the present study, we analyzed the effects of ontogenetic quinpirole treatments on female rats to analyze whether enhancement of dopaminergic function would also produce similar behavioral changes in females as has been observed in male animals.

2. Experiment 1

The focus of this experiment was to investigate the effects of ontogenetic quinpirole treatment on MWT performance. First, animals were tested on the standard version of the task, in which the platform remains stationary throughout training. Second, rats were tested on the matching-to-place version, in which the platform is placed in a different location daily across 4 days of training. It has been hypothesized that the standard version of the MWT is a test of reference memory, with information remaining constant throughout training (Gerlai, 2001; Poucet, 1993). Based on the fact that there is new information on each day of training, the matching-to-place version of the MWT has been hypothesized to test working memory (Brandeis et al., 1989; Poucet, 1993). In this experiment, we expected that animals receiving ontogenetic quinpirole treatments would demonstrate cognitive deficits relative to saline-

treated controls based on the long-term dopaminergic dysfunction produced by this treatment (Eiant and Szechtman, 1993; Kostrzewa and Brus, 1991; Kostrzewa et al., 1990, 1993a,b).

2.1. Subjects and drug treatment

Subjects in this study consisted of two groups of eight female Sprague–Dawley rats obtained from two litters and weaned at PD 21. Male pups were present during the preweanling period. Half the rats of each litter were behaviorally sensitized with quinpirole HCl treatments (1 mg/kg/day ip) from PD 1 to 11, and the other half received saline in place of quinpirole (1 ml/kg). After PD 21, rats were housed two per cage in a climate-controlled vivarium with a 12-h on/12-h on–off light/dark cycle. Behavioral testing was initiated at approximately PD 60. Food and water were available ad libitum.

2.2. Behavioral procedure: MWT

The water tank used for the MWT measured 1.45 m in diameter and 58.4 cm in height. The water tank was made of galvanized steel, with the interior painted white to better visualize the animal during behavioral testing. A round platform 12.7 cm in diameter and 38.1 cm in height was placed centrally in the southwest quadrant of the pool. The platform was constructed of standard plastic PVC pipe and weighted to maintain the platform underneath the surface of the water. Water was colored opaque using powdered milk and was maintained at 19–21 °C during all behavioral testing. The pool was surrounded by several extramaze cues, including several posters, a video monitor, two waste baskets that could be seen from the surface of the pool and the experimenter, always dressed in a white labcoat and sitting at the "south" release point.

Rats began behavioral testing on the MWT at approximately PD 60. All rats were trained first on the standard version of the task, with the platform stationary throughout training. In this version, rats were given eight training trials per day over 3 consecutive days, with a trial consisting of the rat being released with its nose pointing towards the wall of the pool on each training trial, and all rats were given 60 s to reach the platform. If an animal reached the platform within 60 s, its time was recorded (*acquisition latency*) and the animal remained on the platform for 10 s. If the rat failed to reach the platform within 60 s, it was placed on the platform by the experimenter. Regardless of whether the rat located the platform on each trial, it spent the last 10 s of each trial on the platform. Immediately after the last training trial on the final day of training, all rats were given a probe trial in which the platform was removed from the pool. On the probe trial, rats were released from the north release point and allowed to swim for 60 s, with swim patterns recorded by a CCD videocamera (Rockhouse Products, NJ) mounted above the pool. The swim patterns were later analyzed on videotape. The dependent measure utilized on the probe trial was the *mean search difference* (MSD) score, which has been described elsewhere (Brown et al., 2000, 2001; Gonzalez et al., 2000). Briefly, the amount of time spent in the quadrant that formerly contained the platform (D) is separately subtracted from the three other quadrants (A, B and C), which did not contain the platform, summed and divided by three. The formula for the MSD score is as follows: $[(D-A)+(D-B)+(D-C)]/3$. The MSD score provides a measure of spatial bias to the former platform location relative to the three other nontarget quadrants. This dependent measure is advantageous to visits to the former platform location alone or search time to the quadrant formerly containing the platform, because the MSD accounts for visits to all four quadrants of the pool.

Two days after completion of training on the standard version, rats began training on the matching-to-place version of the MWT. In this version, rats were given two daily training trials for 4 consecutive days, with the platform moved to a new location each day. Throughout training, the platform was always randomly placed in one of the four quadrants, and rats were released from the most distant release point from the platform on each training trial and acquisition latency was recorded.

2.3. Data analysis

All data were analyzed using an analysis of variance (ANOVA) statistical test, and Fisher LSD post hoc analyses were used where appropriate ($P=.05$).

2.4. Results

Acquisition latency results for the standard version of the MWT are shown in Fig. 1. Acquisition data were analyzed over six trial blocks. The six trial blocks are shown along the x-axis, and each of these trial blocks consisted of four training trials. Within each trial block, the animal was

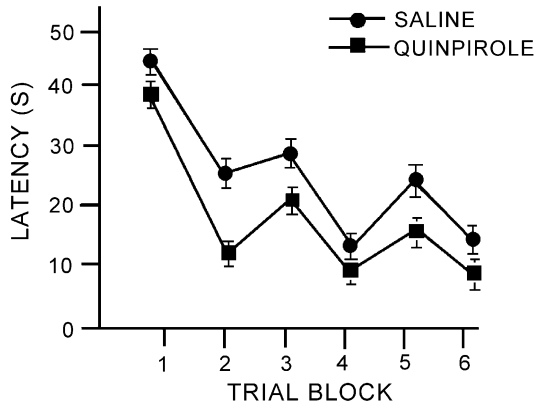

Fig. 1. Acquisition latency results, standard version of the MWT, Experiment 1. Acquisition latency is presented as a function of trial block, which is an average of the latency to locate the platform on four consecutive training trials.

released once from each of the four release points (N, W, S and E), and the data point for each trial block is a mean of the latency to locate the platform for the four trials within that trial block. A two-way repeated-measures ANOVA revealed a significant main effect of trial block [$F(1,5)=18.56$, $P<.01$] but did not reveal a significant main effect of drug treatment group ($P=.12$). Although it appears through observation that the quinpirole group may reach the platform significantly faster than the saline-treated controls, this was not confirmed by statistical analysis.

Probe trial results for the standard version of the MWT are shown in Fig. 2. A one-way ANOVA of the MSD score revealed a significant main effect of drug treatment group [$F(1,12)=12.80$, $P<.01$]. Rats ontogenetically treated with quinpirole spent significantly less time in the quadrant that formerly contained the platform than saline-treated controls, showing that ontogenetic quinpirole treatment produced deficits in probe trial performance of the standard version of the MWT.

Results for the matching-to-place version of the MWT are shown in Fig. 3. There are two trials represented in the figure, with Trial 1 representing the mean of the first of the two daily trials on this task, averaged across all 4 days of training. Trial 2 in the figure represents the mean of the second of the two daily trials on this task, also averaged across all 4 days of training. A two-way repeated-measures ANOVA revealed a significant training trial main effect [$F(1,12)=9.38$, $P<.01$], but the group main effect was not significant ($P=.23$) nor was the Group×Trial interaction, although it approached significance ($P=.07$). It appears that ontogenetic quinpirole treatment affects performance on the standard but not the matching-to-place version of the MWT.

2.5. Discussion

Findings from this experiment demonstrate that ontogenetic quinpirole treatments (1) produce deficits on probe trial performance given at the end of behavioral training on the standard version of MWT and (2) do not affect performance on the matching-to-place version of the MWT. Similar to that of other rodent models of dopamine hyperfunction, ontogenetic quinpirole treatments produced deficits on a cognitive task (Szechtman et al., 2001). Interestingly, ontogenetic quinpirole treatments did not produce a deficit in performance of the matching-to-place task, suggesting that the deficits produced by this drug treatment are specific to the searching ability required to return to a learned location in an open-field spatial task. The exact manner in which an animal learns the location of a hidden platform in the water maze has been argued in several past studies (Gerlai, 2001; Poucet, 1993; Whishaw et al., 1995) but suffice it to say that an animal must use complex extramaze cue associations (Gerlai, 2001) or path integration (Whishaw et al., 1995) to return to the former platform location on the probe trial. In this experiment, it appears that ontogenetic quinpirole treatments has produced a deficit in one or possibly both of these cognitive abilities.

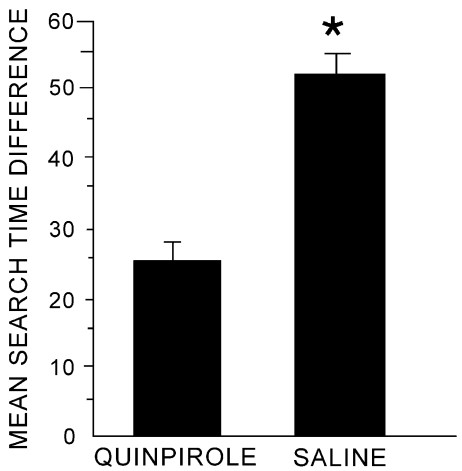

Fig. 2. Probe trial results, standard version of the MWT, Experiment 1. MSD scores as a function of group.

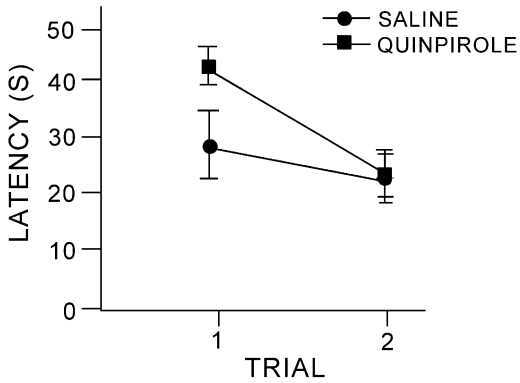

Fig. 3. Matching-to-place task results, Experiment 1. Acquisition latency is presented as a function of trial.

The results of the MSD score of the probe trial show that control animals demonstrate a strong spatial bias to the quadrant, which formerly contained the platform. In fact, the maximum score on the MSD measure is 60, and controls scored slightly less than this maximum score. Quinpirole-treated rats clearly demonstrated a bias to the former target quadrant (the MSD score would equal zero if there were no spatial bias). However, their performance was significantly less than controls. The performance of quinpirole-treated rats is similar to that of rats given brain lesions, in that lesioned rats will also demonstrate a bias to the former target quadrant. However, this bias is significantly less than non-lesioned controls. It has generally been recognized that animals that show a stronger spatial bias to the former platform location on the MWT are demonstrating a stronger cognitive representation for the former platform location (Brandeis et al., 1989; Day and Schallert, 1996). This may seem counterintuitive, based on the fact that an animal that has knowledge for the former platform location should be able to recognize that the platform is not located in its former

location during the probe trial, visit this location once and search elsewhere. However, this is clearly not the case when control animals are tested on this task. Numerous studies have shown control animals to perseverate in the former target quadrant and repeatedly visit the former platform location (Brandeis et al., 1989; Day and Schallert, 1996; Gerlai, 2001). In the present study, it is argued that control animals clearly have a stronger cognitive representation for the former platform location than ontogenetically quinpirole-treated rats. Ontogenetic quinpirole treatment has not alleviated the ability to form this cognitive representation but has simply lessened the animal's ability to form a cognitive representation that is as strong as controls on the reference memory or standard version of the MWT.

There were no statistical differences between groups on the matching-to-place version of the MWT. It has been suggested that the matching-to-place version of the MWT is a measure of working memory, but this may not be the case (Morris et al., 1986). It could be that the matching-to-place task is a test of learning a motor strategy to locate the platform. Logically, this may be the most appropriate strategy to adopt in this situation because extramaze cues have essentially been rendered irrelevant by the changing platform location, and the most successful strategy could be to simply circle a particular distance from the wall of the pool. Through observation, it was noted that animals tended to adopt a circling strategy, certainly on the first daily training trial. The second daily training trial could be a measure of the animals' memory for the platform location learned from the first trial or a measure of the motor strategy adopted during training. Results showed that quinpirole-treated animals did not demonstrate a deficit in learning of the motor strategy required for this version of the MWT. Therefore, the cognitive deficit produced by ontogenetic quinpirole treatment is specific to the cognitive mechanisms underlying performance on the reference memory version of the MWT.

3. Experiment 2

The focus of this experiment was to investigate the effects of ontogenetic quinpirole treatment on reaching accuracy and locomotor activity. In rodent models of dopaminergic hyperfunction, there has been little information relative to the effects of brain lesions on motor tasks that require reaching accuracy. However, past research suggests that early quinpirole treatment may have an effect on reaching accuracy, based on studies that have shown that this treatment produces prolonged supersensitization of the D_2 receptor. With the important role the dopaminergic system plays in motor performance, it seems likely that this treatment may produce an enhancement in reaching accuracy. In fact, quinpirole has been shown to alleviate motor deficits produced by unilateral 6-hydroxydopamine (6-OHDA) lesions of the striatum (Olsson et al., 1995). Additionally, Fricker et al. (1997) have shown that increased binding to the D_2 receptor also increased recovery on the staircase motor test after an excitotoxic lesion to the striatum, indicating that the D_2 receptor plays an important role in a skilled motor task. Therefore, it was our hypothesis that ontogenetic quinpirole treatment would increase skilled reaching accuracy and produce increased locomotor activity in adult female rats.

3.1. Subjects and behavioral procedure: Whishaw reaching task

The same rats from Experiment 1 served as subjects in this experiment. Behavioral testing on the Whishaw reaching task began 2 weeks after completion of behavioral testing on the MWT.

Structural design and the behavioral training procedure used for this experiment were based on Whishaw and Metz (2000) with some slight modifications (see Fig. 4). The reaching boxes were made of clear Plexiglas ($45 \times 50 \times 15$ cm) and placed above a floor of paperboard. In the middle of the front wall, a 1.9-cm wide vertical opening allowed the animals to reach for the pellets placed on a shelf (see Fig. 4), which was attached to the front wall and positioned 4 cm above the floor. A small food well, centered in the middle of the vertical opening, served to hold the sucrose pellet in place. Distance between the food well and front wall was 1.5 cm.

All rats were maintained at 85% of their full body weight throughout training. Before behavioral training was to

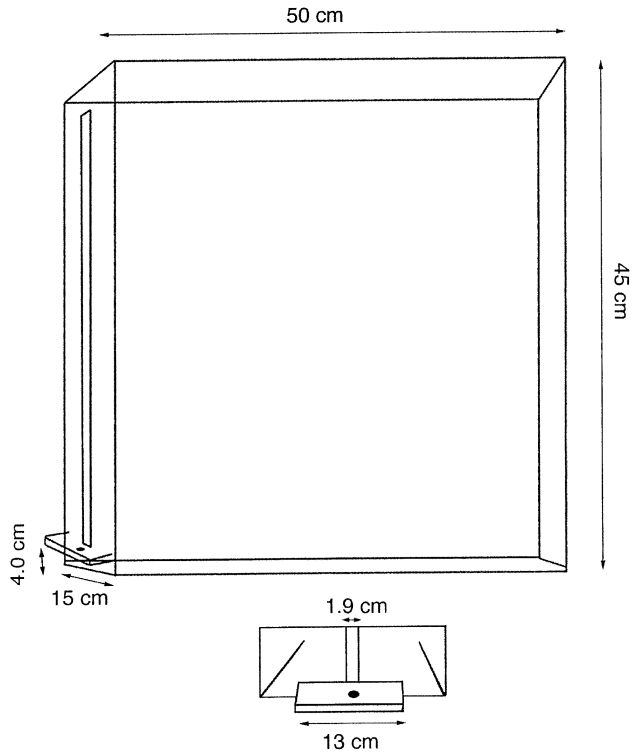

Fig. 4. Depiction of the reaching apparatus adapted from Whishaw and Metz (2000).

begin, all rats were habituated to the apparatus for 1 day, which consisted of the animal being placed into the reaching box for 10 min. On the day following habituation, rats were given pretraining in which they reached for a 45-mg food pellet (Noyes, Lancaster, NH) on 5 consecutive days. These pellets were not novel to the animal, because rats had been fed these pellets for 2 weeks previous to training on the reaching task. Rats received 20 food pellets for each pretraining day, and it should be noted that all rats attempted to obtain all 20 food pellets on the first day of pretraining. Pellets were presented one at a time in the food well with forceps and attention was paid to placing it in the center of the food well for each reaching attempt. All animals' success rates were stable by Day 4. Behavioral training began 1 day after the habituation/pretraining session and continued for 15 days. Rats were tested 5 days/week. On each day of training, rats were presented with 20 food pellets and each trial was scored as a *success* or a *miss*. A *success* was defined as a reach on which an animal grasped a food pellet, transported it with the paw into the cage and placed it into its mouth. A *miss* was defined as a reach in which an animal advanced the paw through the vertical opening but missed the pellet, knocked it away or dropped the pellet as it was brought back through the vertical opening. Reaching performance was scored as the percentage of successful reaches following the formula of Whishaw and Metz (2000): (number of successful reaches)/(number of successful reaches + number of missed reaches) × 100.

3.2. Locomotor activity

Locomotor activity testing began 4 days after completion of the reaching task, and animals were not food deprived during the activity sessions. The square arena used for activity was made of black Plexiglas, measuring 90 cm on a side. On the floor of the arena was a grid of white lines, 12 cm apart. This grid of lines covered the entire floor of the arena. Rats were placed into the arena for three 10-min sessions, once a day for 3 consecutive days. Above the arena was a videocamera, connected to a monitor that was located in a separate room. Horizontal activity was measured in 10 1-min bouts per session by an observer watching the monitor and each line crossing was scored by the observer. Vertical movement was scored by recording each rearing movement. A fan in the room with the activity box was used to mask outside noise.

3.3. Results

3.3.1. Whishaw reaching task

The percentage of successful reaches is presented in Fig. 5. Training data were analyzed in five blocks, with each block consisting of three daily sessions. A two-way repeated-measures ANOVA revealed a significant main effect of group [$F(1,48) = 5.04$, $P < .03$] and session [$F(4,48) = 11.96$, $P < .01$]. Fisher's LSD post hoc tests revealed that the quinpirole group demonstrated superior reaching accuracy compared to saline-treated controls at training blocks 2 and 3, which corresponds to training days 4–10. It appears from this result that ontogenetic quinpirole treatment enhances skilled reaching accuracy relative to saline controls.

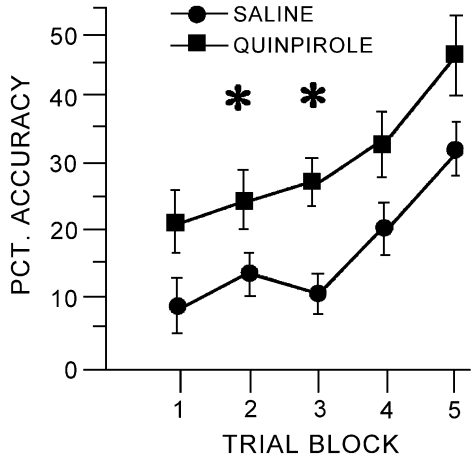

Fig. 5. Whishaw reaching task results, Experiment 2. Reaching accuracy is presented as a function of trial block, which is an average of three consecutive daily training sessions.

3.3.2. Locomotor activity

Horizontal locomotor activity is shown in the top panel of Fig. 6, with rearing represented in the bottom panel. A one-way ANOVA revealed a significant group main effect for horizontal activity [$F(1,12) = 5.15$, $P < .04$] and rearing [$F(1,12) = 4.54$, $P < .05$]. Rats ontogenetically treated with quinpirole demonstrated a significantly higher amount of activity than saline-treated controls.

3.4. Discussion

The results of this experiment revealed that ontogenetic quinpirole treatments (1) enhanced reaching accuracy and (2) produced hyperlocomotion in adulthood. A possible explanation for the significant increase in reaching accuracy may be that ontogenetic quinpirole treatments produced supersensitization of D_2 receptors, which may aid motor accuracy. One possible mechanism is that ontogenetic quinpirole treatments produce central nicotinic receptor up-regulation (Tizabi et al., 1999), and this up-regulation may be occurring at the neuromuscular junction, where nicotinic receptors are prevalent (Bowman et al., 1990). Although it seems logical that increased synaptic efficacy at the neuromuscular junction could enhance skilled reaching accuracy, it is not known if quinpirole produces nicotinic receptor up-regulation in the periphery.

An important issue in this experiment concerns the poor overall performance of all rats on the skilled reaching task. Prior studies have shown that Long–Evans hooded rats demonstrate performance at an 80% success rate or better on this task (Whishaw and Metz, 2000), whereas the success

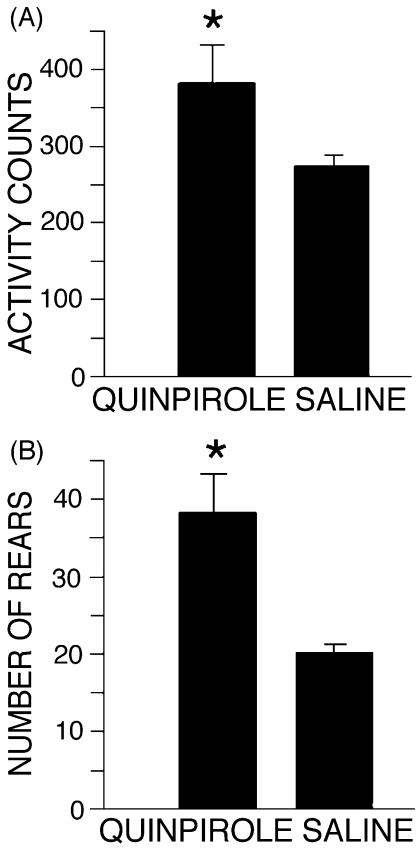

Fig. 6. Locomotor activity results, Experiment 2. (A) Line crossings, denoted as activity counts, are presented as a function of group. (B) Vertical rears are presented as a function of group.

rate in this experiment reached an asymptote of 50% in the animals treated with quinpirole and only after 20 days of pretraining and training. Prior research has shown that Sprague–Dawley rats have poor visual acuity compared to Long–Evans hooded rats (Birch and Jacobs, 1979), and this may be an important factor in the rats' overall performance.

The result of overall increased locomotor activity is consistent with past studies on the effect of ontogenetic quinpirole treatments (Szechtman et al., 2001) and past results of Kostrzewa et al. (1990, 1993a,b) that have shown ontogenetic quinpirole treatments produce hyperlocomotion in adulthood. The increase in activity is likely to be due to the functional changes at the D_2 receptor, because neuroleptics such as haloperidol that block the D_2 receptor have been shown to block this hyperactivity in adulthood (Kostrzewa et al., 1990).

4. General discussion

The present findings demonstrate that ontogenetic quinpirole treatments produce long-term effects on behavior in adulthood, including cognitive deficits on the water maze, but enhancement of skilled reaching accuracy and an overall increase of locomotor activity. Quinpirole is a highly selective D_2/D_3 agonist, and ontogenetic quinpirole treatments not only produce functional changes in the D_2 receptor but also modulate other neurochemical responses, such as nicotinic receptor up-regulation (Tizabi et al., 1999). The changes produced in other neurochemical systems imply that dopaminergic dysfunction may be only one aspect of the underlying neurological mechanisms of the behavioral changes produced by dopaminergic hyperfunction, and this issue has been discussed in past studies (Carlsson, 2000; Depatie and Lal, 2001; Goodman and Pardee, 2000; Harvey et al., 2001; Thacker and Carpenter, 2001; Umegaki et al., 2001; Zitterl et al., 2001). Regardless, the functional changes in neurochemistry produced by ontogenetic quinpirole treatments produce long-term changes in behavior in adulthood, suggesting that this may be a reasonable model for behavioral disorders produced by dopaminergic dysfunction.

In Experiment 1, ontogenetic quinpirole treatments did not produce a deficit on acquisition latency but did produce a deficit on probe trial performance. Although this may seem contradictory, several studies have demonstrated a dissociation between acquisition latency and probe trial performance in rats that received a brain insult (Gerlai, 2001; Scheff et al., 1997; Whishaw et al., 1995). Specifically, given the appropriate training procedures, rats have been shown to not demonstrate deficits on acquisition latency but show poor performance on the probe trial at the end of training. Whishaw et al. (1995) have distinguished between the ability to reach the platform during acquisition and probe trial performance. In essence, rats can learn a strategy to navigate to the platform during acquisition, such as a motor or landmark strategy, but not necessarily have a cognitive representation of where the platform is located. If an animal has memorized a strategy and the probe trial is administered, the strategy of memorizing a strategy to reach the platform location will fail once the animal reaches the former platform site. Conversely, a rat with knowledge of the former platform location on the probe trial can revert to several different strategies, including extramaze cue associations, path integration and other previously successful search strategies. In this experiment, it appears that rats given ontogenetic quinpirole treatment were able to learn a specific strategy to locate the platform during acquisition but not have the ability to integrate these strategies on the probe trial.

The performance deficits on the MWT produced by ontogenetic quinpirole treatments could be produced by a number of mechanisms. Prior studies have shown that quinpirole, administered from PD 1 to 21 (a period of 10 days longer than the present study), produced a robust increase in α_7, but not $\alpha_4\beta_2$, nicotinic receptors in the hippocampus in rats at 30 days of age (Tizabi et al., 1999). Nicotinic receptor up-regulation suggests possible cholinergic hypofunction in the septohippocampal pathway. In essence, it could be that a lack of acetylcholinergic activity in the hippocampus may produce an overall up-regulation of nicotinic receptors. If this

is the case, this could be a possible underlying mechanism for the deficits in MWT performance demonstrated in rats ontogenetically treated with quinpirole. The effect of ontogenetic quinpirole treatments on nicotinic receptor expression in adult rats is not known, but it appears that ontogenetic quinpirole produces a modulatory effect on the acetylcholinergic system in the hippocampus. One possible mechanism through which ontogenetic quinpirole treatments may be acting is through producing an increase in corticosterone release when administered during development. Quinpirole has been shown to produce a significant increase in plasma corticosterone and decreases hippocampal brain-derived neurotrophic factor (BDNF) in adulthood (Borowsky and Kunn, 1992; Fumagalli et al., 2001). Both of these neurotrophins have been shown to play important roles in hippocampal development, and an increase in corticosterone during critical developmental periods could produce developmental abnormalities and long-term neuropathology in the hippocampus (Schaaf et al., 1998, 2001). Future experiments will be focused on attempting to better understand the underlying mechanism of quinpirole's modulation of the acetylcholinergic system.

There has been one past study to analyze the effects of chronic quinpirole treatment on spatial learning in the MWT with behavioral testing performed after completion of quinpirole-induced locomotor sensitization. Eiant and Szechtman (1993) demonstrated that rats sensitized to quinpirole (0.5 mg/kg given every 4 days) produced a significant preference for the quadrant formerly containing the platform on a probe trial given at the end of training compared to saline-treated controls. Although these findings contradict the findings of the current study, there are several critical methodological differences between the two studies that may account for this contradiction. The most critical difference between these two studies is that in the study by Eiant and Szechtman (1993), *adult* rats were sensitized to quinpirole and later tested on the MWT. In the present study, quinpirole was given ontogenetically and during a critical period of brain development. We hypothesize that the deficits observed in this study may be due to increased plasma corticosterone levels produced by quinpirole (Fumagalli et al., 2001). The effects on brain structures produced by quinpirole sensitization would clearly be different in adult rats compared to the drug being administered during critical periods of brain development. Quinpirole administration in adult animals has been shown to stimulate acetylcholine release in the ventral hippocampus, which correlates with an enhancement of cognitive performance (Umegaki et al., 2001). It has also been demonstrated that chronic psychostimulant administration before MWT training produces an enhanced perseveration for the former platform location on the probe trial (Brown et al., 2000, 2001) and quinpirole is clearly producing a similar effect. Whether or not the increased perseveration in former target quadrant is an actual enhancement of cognitive performance is arguable, and as Eiant and Szechtman (1993) have suggested, this may be a demonstration of compulsive behavior in adult rats produced by quinpirole sensitization.

With the finding that ontogenetic quinpirole treatment produces cognitive deficits, future studies will be focused on attempting to alleviate these deficits. Because of the ability of nicotine to enhance cognitive abilities and to accelerate recovery of behavioral function after brain injury (Bowman et al., 1990; Brandeis et al., 1989; Decker et al., 1992; Levin et al., 1997), future studies will explore the effect of the administration of nicotine in adult rats ontogenetically treated with quinpirole to attempt to alleviate the cognitive deficits produced by dopaminergic dysfunction associated with this treatment.

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