

Ming Li · Radek Budin · Alison S. Fleming ·
Shitij Kapur

Effects of novel antipsychotics, amisulpiride and aripiprazole, on maternal behavior in rats

Received: 24 May 2005 / Accepted: 25 May 2005 / Published online: 16 July 2005
© Springer-Verlag 2005

Abstract *Rationale:* Rat maternal behavior, which entails complex motivational and social factors, is disrupted by the currently available typical and atypical antipsychotics. It is thought that this disruption reflects a side effect of antipsychotics, modeling the neuroleptic-induced negative or deficit state. Amisulpiride and aripiprazole are new atypical antipsychotics with mechanisms of action distinct from the current typical and atypical antipsychotics. The effects of these drugs on maternal behavior have not been explored. *Objective:* In the present study, we systematically examined the behavioral effects of amisulpiride and aripiprazole on maternal behavior in postpartum female rats. *Methods:* Various components of maternal behavior (pup retrieval, pup licking, nest building and pup nursing) were examined repeatedly over a period of 24 h after a single injection of three doses of amisulpiride (10, 30, and 100 mg/kg s.c.) and aripiprazole (3, 10, and 30 mg/kg). *Results:* Amisulpiride at the lower doses (10 and 30 mg/kg) enhanced pup licking, and only at the highest dose disrupted the active components of maternal behavior such as pup retrieval and nest building. Its effect was delayed in onset and prolonged as compared to other antipsychotics. Aripiprazole, even at the highest dose (30 mg/kg) did not impair pup retrieval or pup licking. However, it did disrupt nest building and led to enhanced pup nursing. *Conclusions:* The unique effects of these two drugs may be due to their unique actions at the mesolimbic dopamine

synapses. The sparing of the major components of maternal behavior by aripiprazole may be related to its partial agonist effects, whereas the enhancement of pup licking by amisulpiride may be related to its dose-dependent preferential effect on the presynaptic autoreceptors. The potential clinical implications of these findings are discussed.

Keywords Amisulpiride · Aripiprazole · Maternal behavior · Motivated behavior · Rat

Introduction

“Atypical” antipsychotic drugs (APDs) such as clozapine, risperidone, olanzapine, and quetiapine are now the drugs of choice to treat schizophrenia and have replaced the conventional “typical” APDs such as haloperidol and chlorpromazine (Kapur and Remington 2001). Recently, two new atypical antipsychotics, aripiprazole and amisulpiride (amisulpiride is available for clinical use in Europe and not as yet in the USA or Canada), have been introduced into clinical practice. Both drugs show efficacy against positive and negative symptoms of schizophrenia, with low incidence to cause extrapyramidal side effects and other side effects such as sedation or weight gain (Boyer et al. 1995; Delcker et al. 1990; Gupta and Masand 2004; Kane et al. 2002; Naber and Lambert 2004). However, their mechanisms of action are distinct from the more widely used atypicals (such as risperidone, olanzapine, and quetiapine). Whereas clozapine, risperidone, olanzapine, and quetiapine are thought to show their atypicality by potently blocking 5-HT_{2A} receptors and showing a high 5-HT₂ to D₂ ratio (Meltzer et al. 2003), amisulpiride and aripiprazole do not. Amisulpiride is a specific dopamine receptor antagonist with high affinities for both dopamine D₂ and D₃ receptor subtypes. It has no other pharmacologically relevant receptor activities (Moller 2003; Perrault et al. 1997; Schoemaker et al. 1997). Its selectivity for limbic areas and preferential blockade of presynaptic dopamine autoreceptors are thought to mediate its low liability for extrapyramidal side effects (Delcker et al. 1990; Moller

M. Li · S. Kapur (✉)
Centre for Addiction and Mental Health,
Clarke Site 250 College Street,
Toronto, Ontario, M5R 1T8, Canada
e-mail: shitij_kapur@camh.net
Tel.: +1-416-5358501

R. Budin · A. S. Fleming
Department of Psychology,
University of Toronto at Mississauga,
Mississauga, Ontario, Canada

S. Kapur
Department of Psychiatry, University of Toronto,
Toronto, Ontario, Canada

2003; Perrault et al. 1997). Aripiprazole shows high affinity for dopamine D₂ receptors. However, in contrast to all previous APDs, it is a partial agonist rather than a full antagonist at these receptors (Aihara et al. 2004; Burris et al. 2002; Kikuchi et al. 1995; Lawler et al. 1999; Shapiro et al. 2003). As a result, it acts as a D₂ receptor agonist at receptor sites where dopaminergic transmission is significantly decreased while acting as an antagonist at other dopaminergic sites with normal or increased transmission. However, because of its intrinsic efficacy, it does not cause total blockade of dopamine transmission even when it occupies all the dopamine receptors (Kikuchi et al. 1995). Although it also has moderate affinities for rat 5-HT_{2A} and 5-HT_{1A} receptors in vitro (Lawler et al. 1999), affinities for these receptors are more than ten times lower than that for the rat dopamine D₂ receptors. Thus, both aripiprazole and amisulpiride have an in vitro profile that does not conform to the standard 5-HT₂/D₂ profile of other atypical APDs (Hirose et al. 2004).

Preclinical behavioral studies have generally focused on the effects of both drugs on simple behavioral responses such as locomotion, grooming, climbing, yawning, stereotypy, lever pressing, and catalepsy (Duarte et al. 2003; Fujikawa et al. 1996; Goudie and Taylor 1998; Hirose et al. 2004; Nakai et al. 2003; Perrault et al. 1997). In recent years, we have used rat maternal behavior—a highly motivated and well-organized social behavior—to evaluate the behavioral effects of APDs on the premise that this model may provide an analog for the study of the complex and multidimensional actions of APDs on affective, cognitive and social functions. We and others have found that acutely administered typical APDs (e.g., haloperidol, pimozide) or atypical APDs such as clozapine, risperidone, and quetiapine disrupt active components of maternal behavior (e.g., pup retrieval, pup licking, and nest building) when given at doses that give rise to brain D₂ receptor occupancy levels that are consistent with doses used in the clinics (Giordano et al. 1990; Li et al. 2004; Silva et al. 2001). Animals under the influence of APDs are slower to approach pups and retrieve fewer pups. They also spend less time licking their offspring and building a nest. Chronic treatment with haloperidol or olanzapine via minipumps or repeated daily injections also significantly inhibits rat active maternal responses (Li et al. 2005). Evidence currently available suggests that the APD-induced disruption on pup retrieval, pup licking, and nest building might be an inherent feature of all APDs (tested to date), regardless of whether they are typical or atypical antipsychotics or whether they are administered acutely or chronically. Furthermore, because the APD-induced maternal behavior deficits bear some similarities to the neuroleptic-induced deficit syndrome (NIDS), which manifests itself as poverty of speech, flattened affect, loss of drive, social withdrawal, etc., these studies may provide some insights into the mechanisms and the relative propensities of the different drugs to cause NIDS in patients.

In the present study we sought to examine what impact amisulpiride and aripiprazole might have on maternal behavior. Because all of the antipsychotic drugs we tested so

far produce a disruption of pup retrieval, pup licking, and nest building, we hypothesized that amisulpiride and aripiprazole would cause a similar disruption of these behaviors. We had no a priori position on their effects on pup nursing because previously tested antipsychotics have shown a mixed effect on pup nursing (some enhance it, some disrupt it, some have no effect). Separate groups of mother rats were given injection of three doses of amisulpiride or aripiprazole on day 6 postpartum and their maternal behavior was observed six to seven times over a period of 24 h (see below for the detailed dose-choosing criteria). This design not only allowed us to observe how amisulpiride and aripiprazole affect maternal behavior dose-dependently, but also permitted description of the time course of their actions. Since a similar testing schedule had been implemented in our previous study (Li et al. 2004), this design also allowed us to compare drug effects in the current study with those observed in our earlier study (clozapine, risperidone, and quetiapine).

Materials and methods

Subjects and housing

Subjects were 60- to 100-day old virgin female Sprague–Dawley rats weighing 250–380 g. They were reared and mated at the Department of Psychology, University of Toronto at Mississauga, from a stock originally obtained from Charles River (St. Denis, Quebec, Canada). The animals were housed individually in opaque plastic cages [47 (L) × 26 (W) × 20 (H) cm] with food (Purina Rat Chow) and tap water ad lib. Wood shavings were provided for bedding. Subjects were maintained on a 12:12-h day–night cycle (lights on at 8:00 A.M.); room temperature was kept at 22°C and humidity was controlled at 45–55%. All procedures were approved by the animal care committee at University of Toronto at Mississauga.

Groups and choice of doses

In an antipsychotic comparison study, dose selection is absolutely crucial. Inappropriate dose choices can lead to misinterpretation of the data and wrong conclusions (Kapur et al. 2000). Therefore, we chose our doses based on the following considerations: (1) chosen doses must provide in animals receptor occupancies comparable to those observed in patients, approximately 65–70% striatal D₂ occupancy (Kapur et al. 2003); (2) doses of aripiprazole and amisulpiride must be active in the conditioned avoidance response model, a model that has high predictive validity for APD clinical potencies (Wadenberg et al. 2000); (3) the range of doses must cover subclinical as well as supra-therapeutic doses. Guided by these principles, we selected doses of 10, 30, and 100 mg/kg of amisulpiride, which give rise to 60, 81, and 87% D₂ occupancies, respectively, at 6 h postinjection (unpublished observations), and 3, 10, and 30 mg/kg of aripiprazole, which give rise to 71, 85, and 84%

D₂ occupancies, respectively, at 1 h postinjection (Reckless et al. 2005). At the medium and high doses, both drugs disrupt conditioned avoidance response (unpublished observations) but do not cause catalepsy (Hirose et al. 2004; Perrault et al. 1997).

A total of 64 female rats were run in two separate experiments ($n=32$) with amisulpiride being tested in the first experiment and aripiprazole being tested in the second. The basic procedure was identical. In each experiment, the subjects were randomly assigned into four groups ($n=8$), with three drug dosage groups and one vehicle group.

Drug injections

Amisulpiride and aripiprazole were custom synthesized with purity greater than 99% (high-performance liquid chromatography, HPLC) and structural conformation was made using infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. Amisulpiride was dissolved in double-distilled water containing 2% (v/v) glacial acetic acid. Aripiprazole was dissolved in a mixed double-distilled water solution containing 30% (v/v) dimethylformamide and 2% (v/v) glacial acetic acid. Injections were made subcutaneously at the back of the neck.

Procedure

All subjects were placed into the cage of a proven stud male for a week to ensure pregnancy. Starting 2 or 3 days before the first possible expected parturition date, the subjects were monitored every morning for signs of parturition. Once the dam was found with pups in the morning (that day was designated as day 1 postpartum), she was transferred into a large transparent maternal observation cage [51 (*L*) \times 40.5 (*W*) \times 21 (*H*) cm] with wood shavings for bedding. Two shredded paper towels were also provided for nesting material. The litter size was culled to six pups (three males and three females with the most visible milk bands). On Day 4 postpartum, all subjects were changed to clean observation cages with their litters. Two shredded paper towels were also added. For amisulpiride, on day 6 postpartum, the first maternal behavior test commenced 0.5 h before drug injections, and the remaining tests were done at 3.5, 4.0, 5.0, and 7.0 h after the drug injections. The first drug test was at 3.5 h postinjection instead of the more standard 0.5 h postinjection because amisulpiride enters the brain via the choroid plexus, and this mechanism of entry is slower than other drugs (Hartter et al. 2003). As mentioned above, our *in vivo* occupancy studies in rats show that even at 6 h postinjection, amisulpiride at 10, 30, and 100 mg/kg still gives rise to 60, 81, and 87% D₂ occupancies, respectively, a level of occupancies comparable to that observed in antipsychotic-treated patients. This kind of testing schedule has also been used by others (Goudie and Taylor 1998). For aripiprazole, on Day 6 postpartum, nursing and pup retrieval behavior tests were conducted six times throughout the

day, with the first one beginning 0.5 h before the drug injections, and the rest being carried out at 0.5, 1, 2, 4, and 6 h after the drug injections. The last nursing and pup retrieval behavior tests were conducted at 24 h after the drug injections (day 7 postpartum).

Maternal behavior tests

On day 6 or 7 (for 24-h time point) postpartum maternal behavior tests were conducted. Each test consisted of two phases. The first was a 5-min "undisturbed" maternal behavior observation (termed the "undisturbed" test phase). Using a laptop computer with an event-recording program (Best Analysis), we recorded the duration of nursing behavior (a rat positioning herself over the pups with legs splayed to accommodate the pups, including high and low crouching over postures), pup body licking (a female opening her mouth and placing its tongue on the body of a pup), pup anogenital licking (licking the anogenital area), and nest building (a rat picking up nesting material in her mouth and transporting it back to the nest site or pushing the material with her forepaws toward the nest site).

The second phase was a 5-min pup retrieval behavior test starting immediately after the first undisturbed test (termed the "pup retrieval" test phase). This phase was initiated by taking the six pups away from the mother, and destroying the nest. Ten seconds later, the pups were placed in the corner of the cage diagonal to the nest site. When the subject picked a pup up in her mouth and carried it back to the nest site, it was referred to as a successful pup retrieval (a score of 300 s was assigned to nonresponders who did not approach or retrieve the testing pups). The total number of pups retrieved was recorded. The occurrence of following behaviors was also recorded, including pup body licking, anogenital licking, nest building, and nursing. After the test, any unretrieved pups were returned to the nest site. The observers were not blind to the drug condition of each subject.

Statistical analysis

The effects of amisulpiride and aripiprazole on maternal behavior were analyzed separately. Data were expressed as mean values \pm SEM, and were analyzed using a factorial repeated measures analysis of variance (ANOVA) with the between-subjects factor being treatment condition (drug: three doses of amisulpiride or aripiprazole vs the vehicles) and the within-subject factor being the test time points (test time: 6 for amisulpiride and 7 for aripiprazole). Two group comparisons were tested using post hoc least significant difference (LSD) tests. To determine the temporal course of the drug effect and to pinpoint when significant differences appeared, one-way ANOVAs were conducted for each test time point, followed by post hoc LSD tests to compare the group differences if necessary. Pup licking (including body licking and anogenital licking), nest building, and pup nursing were analyzed and presented sep-

arately for each test phase. A conventional two-tailed level of significance at the 5% level was required.

Results

Effects of amisulpiride treatment on maternal behavior

Figure 1a shows the results of amisulpiride treatment on pup retrieval at each test point in comparison to the vehicle group. Amisulpiride showed a clear disruptive effect on pup retrieval. Drug \times Test Time repeated measure ANOVAs revealed that there was a main effect of drug [$F(3,28)=33.873$, $p=0.000$], a main effect of test time [$F(5,140)=10.77$, $p=0.000$], and a significant Drug \times Test Time interaction [$F(15,140)=6.346$, $p=0.000$]. Post hoc tests indicated that the amisulpiride 100-mg/kg group was significantly different from the other three groups (all $ps<0.001$). To identify the time point(s) at which amisulpiride-treated rats differed from vehicle-treated rats,

one-way ANOVAs were used followed by post hoc LSD tests. Results showed that amisulpiride 100 mg/kg significantly disrupted pup retrieval at 4 h ($p=0.011$), 5 h ($p=0.000$), 7 h ($p=0.000$), and even 24 h after injections ($p=0.001$). No significant difference was found among the amisulpiride 10 and 30 mg/kg and vehicle groups (all $ps>0.05$).

The effects of amisulpiride on pup licking are shown in Fig. 2a. It appears that at the low or medium dose (10 and 30 mg/kg), amisulpiride tended to increase pup licking, whereas at the high dose (100 mg/kg), it tended to decrease it. These effects were more conspicuous during the pup retrieval test phase than during the undisturbed test phase. Statistical analysis confirmed this observation. During the pup retrieval phase, Drug \times Test Time repeated measure ANOVAs followed by post hoc LSD tests revealed that amisulpiride at both 10 and 30 mg/kg significantly enhanced pup licking (all $ps<0.022$ in comparison to the vehicle group). Examination of the time course of the drug's action suggested that their enhancement effects were

Fig. 1 The number of pups retrieved (mean \pm SEM) during the 5-min pup retrieval tests at various testing time points. Effects of three doses of amisulpiride (a) and aripiprazole (b) are shown. Each graph includes data from the corresponding vehicle group as comparison. * $p<0.05$, indicates a significant difference from the vehicle group on that test point

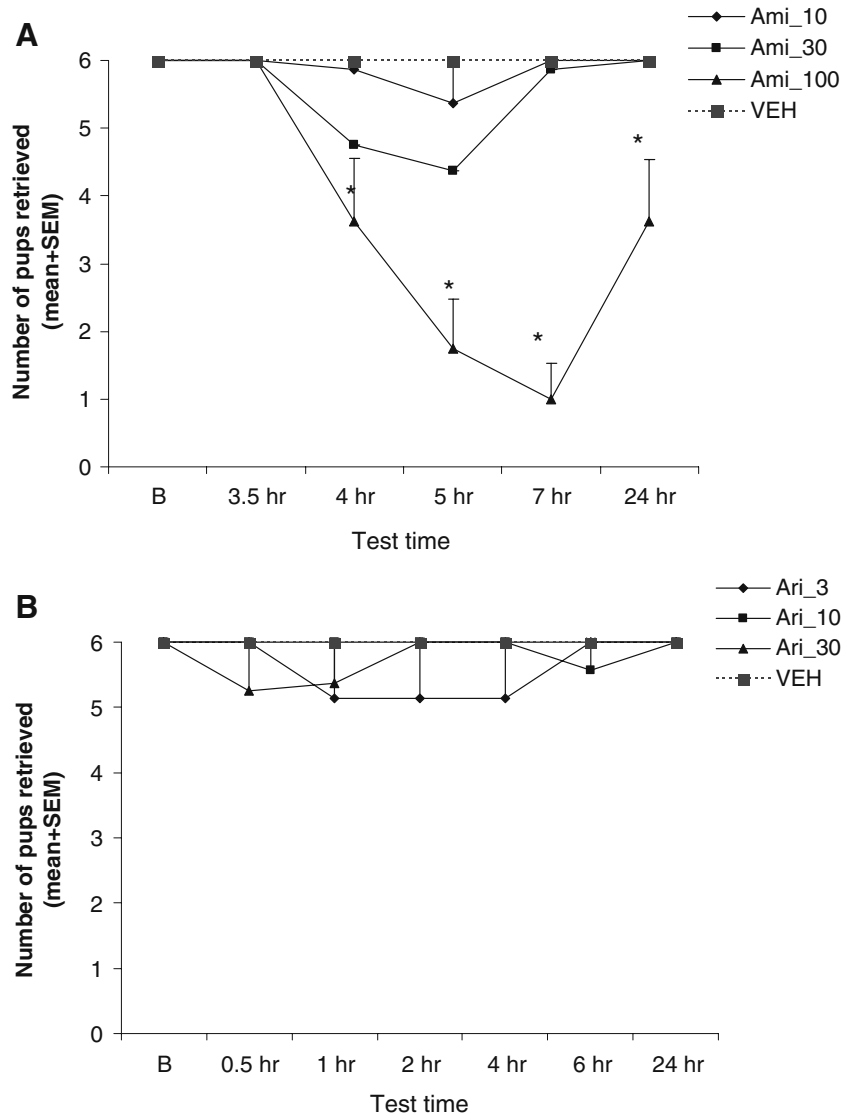
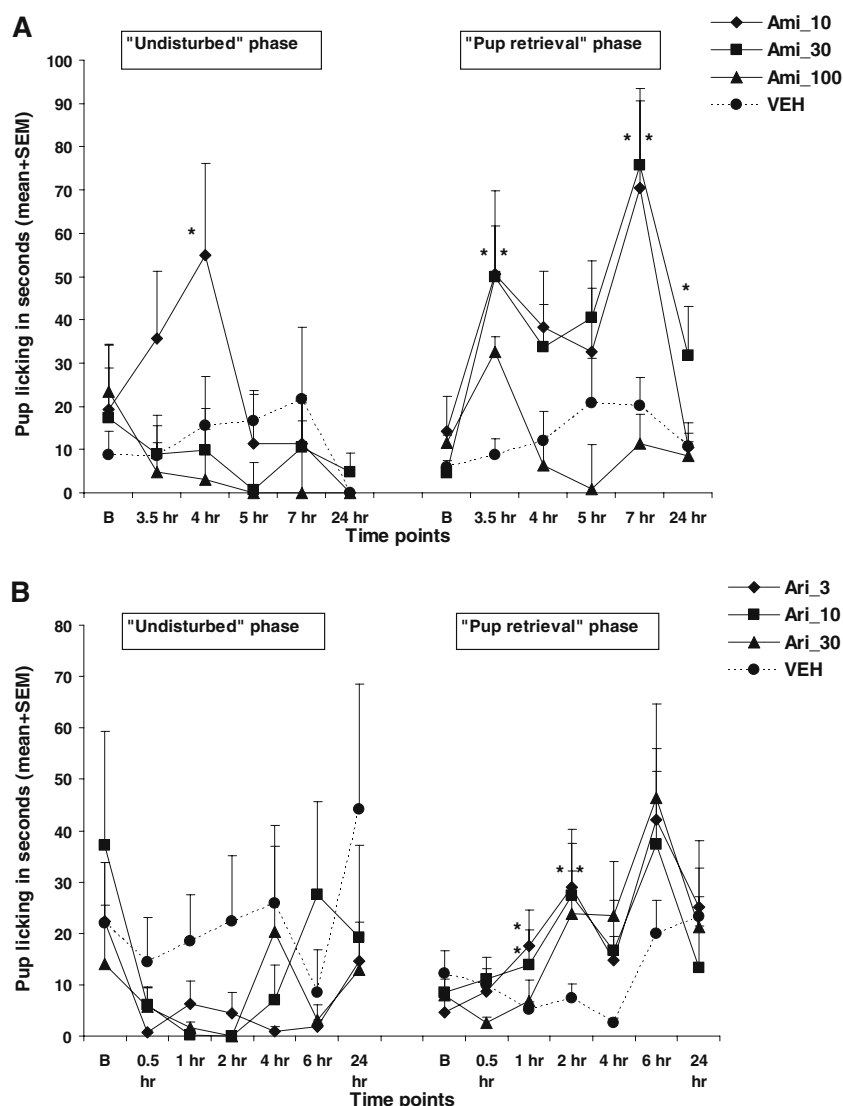


Fig. 2 Pup licking activity (the sum of body and anogenital licking in seconds, mean±SEM) during the 5-min of “undisturbed” test and 5-min of “pup retrieval” test at various testing time points. Effects of three doses of amisulpiride (**a**) and aripiprazole (**b**) are shown. Each graph includes data from the corresponding vehicle group as comparison. * $p<0.05$, indicates a significant difference from the vehicle group on that test point



seen at 3.5 h ($p<0.025$) and 7 h postinjection ($p<0.020$), and the effect of 30 mg/kg was still significant at the 24-h point ($p=0.032$). During the undisturbed test phase, 10 mg/kg amisulpiride significantly enhanced pup licking at the 4-h point ($p=0.04$). In contrast, amisulpiride 100 mg/kg did not enhance pup licking, but rather marginally disrupted pup licking at the 5-h test point ($p=0.088$).

As can be seen in Fig. 3a, nest-building activity rarely occurred during the undisturbed test phase. It was mainly observed in the pup retrieval test phase, during which amisulpiride clearly showed an inhibitory effect throughout the entire test period (Fig. 3a). Drug \times Test Time repeated measure ANOVAs followed by post hoc tests indicated that all three amisulpiride-treated groups significantly differed from the vehicle group (all $ps<0.003$). Their nest building activities were significantly lower at each test point after injections (all $ps<0.040$, except amisulpiride 10 mg/kg at the 24-h point).

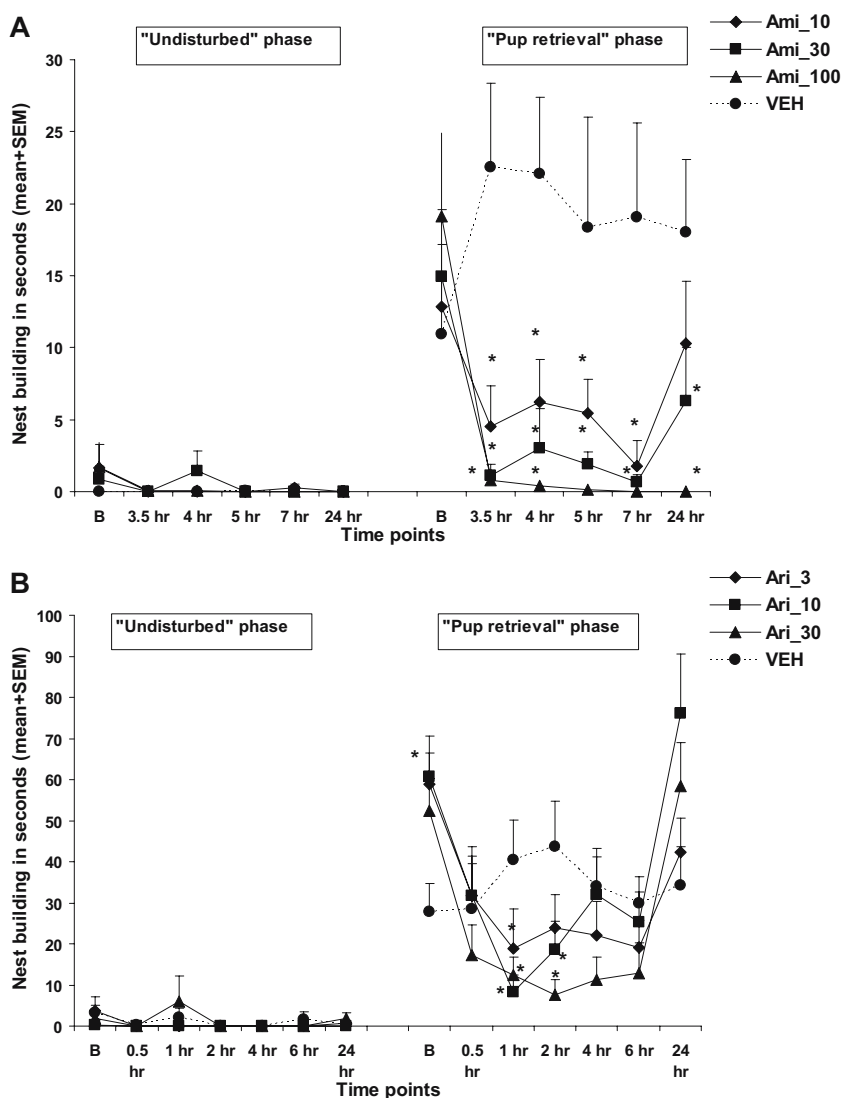
In contrast to the strong effects of amisulpiride treatment on active maternal responses, the drug had no significant effect on the passive maternal behavior, i.e., pup nursing

during both test phases [undisturbed phase: no main effect of drug, $F(3,28)=1.557$, $p=0.222$; no Drug \times Test Time interaction, $F(15,140)=1.142$, $p=0.325$; pup retrieval phase, no main effect of drug, $F(3,28)=2.399$, $p=0.09$; no Drug \times Test Time interaction, $F(15,140)=1.525$, $p=0.104$] (Fig. 4a).

Effects of aripiprazole treatment on maternal behavior

Repeated measures ANOVAs revealed that aripiprazole did not significantly disrupt pup retrieval [Fig. 1b; main effect of drug, $F(3,28)=0.912$, $p=0.448$; Drug \times Test Time interaction, $F(18,168)=0.880$, $p=0.603$], nor did it generally affect pup licking during both test phases (Fig. 2b, no main effect of drug or Drug \times Test Time interaction, all $ps>0.09$). In fact, drug treatment slightly increased pup licking at some test points (see Fig. 2b at 1- and 2-h test points during the pup retrieval phase, $ps<0.028$ from one-way ANOVA LSD post hoc tests comparing the 10- or 30-mg/kg group with the vehicle).

Fig. 3 The duration of nest building (mean±SEM) during the 5 min of “undisturbed” test and 5 min of “pup retrieval” test at various testing time points. Effects of three doses of amisulpiride (a) and aripiprazole (b) are shown. Each graph includes data from the corresponding vehicle group as comparison. * $p<0.05$, indicates a significant difference from the vehicle group on that test point



In contrast, aripiprazole did significantly decrease nest-building activity during the pup retrieval test phase, and this effect depended on when the tests were conducted [Drug \times Test Time interaction, $F(18,168)=3.441$, $p=0.000$]. Examination of the time course for the effects of aripiprazole indicated that the three drug groups each showed significantly higher nest-building activities during baseline, suggesting a sampling bias (all $ps<0.05$). Despite this, at the 1-h test point, all three drug groups showed significantly lower nest-building activities than the vehicle group (all $ps<0.049$). This aripiprazole-induced decrease in nest-building activity was still apparent at the 2-h test point in the 10- and 30-mg/kg groups (all $ps<0.03$), but not the 3-mg/kg group ($p=0.084$).

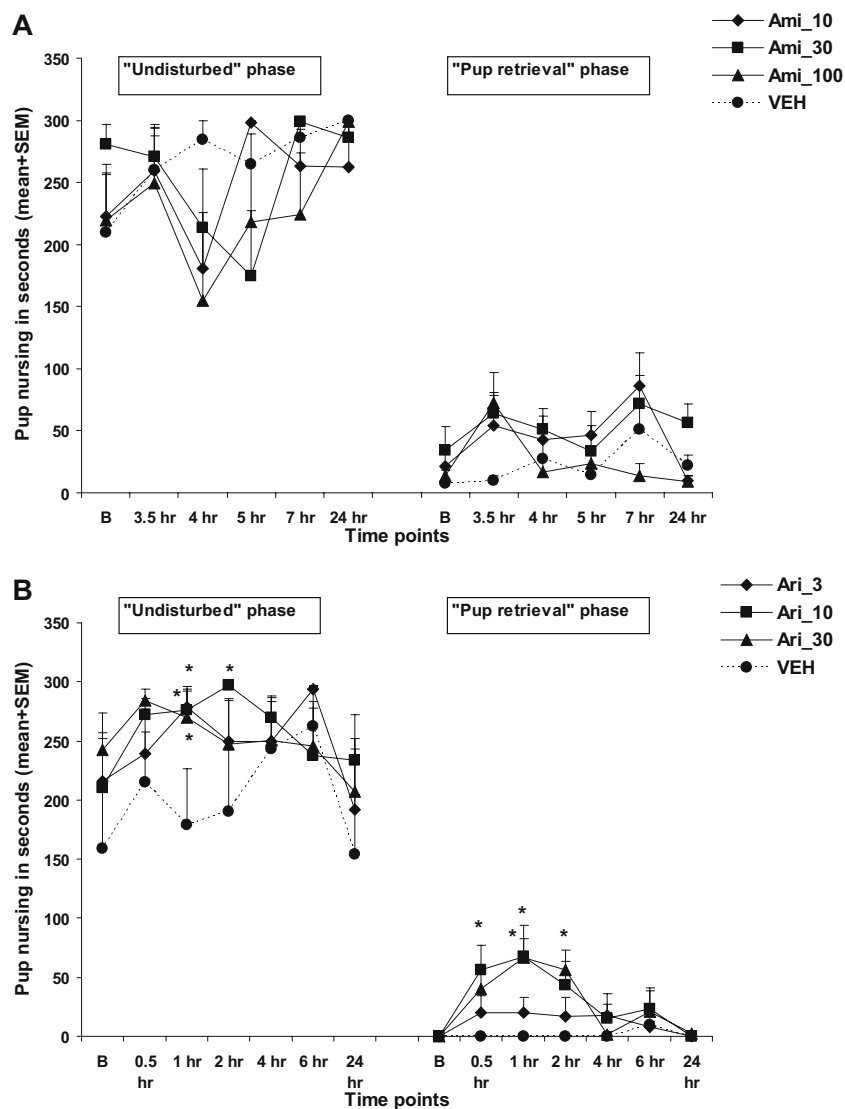
In contrast to the disruptive effect of aripiprazole on nest building, there was an enhancement level of pup nursing in animals treated with this drug (Fig. 4b). Aripiprazole significantly prolonged pup nursing duration during both test phases. During the undisturbed test phase, all three doses of aripiprazole significantly enhanced pup nursing (all $ps<0.030$ in comparison to the vehicle group), where-

as during the pup retrieval test phase, only the medium and high doses of aripiprazole significantly enhanced pup nursing (all $ps<0.016$). Examination of the time course of the drug's action suggested that the enhancement effect of 10 and 30 mg/kg appeared at the 1- and 2-h test points (all $ps<0.05$) and the effect of 3 mg/kg only at the 1-h point during the undisturbed test phase ($p=0.023$). This effect was no longer present 4 h after the drug injections, reflecting its transient nature.

Discussion

The results of the present study point to several novel findings of interest. First, newer atypicals with distinctive mechanisms of action, such as aripiprazole and amisulpiride, do not affect maternal behavior in the same manner as the more conventional typical or atypical antipsychotics (see below). Second, amisulpiride showed a dose-dependent action on pup licking, with low doses (10 and 30 mg/kg) enhancing this behavior, whereas a higher dose (100 mg/kg)

Fig. 4 The duration of pup nursing (including both high and low crouching, mean±SEM) during the 5 min of “undisturbed” test and 5 min of “pup retrieval” test at various testing time points. Effects of three doses of amisulpiride (**a**) and aripiprazole (**b**) are shown. Each graph includes data from the corresponding vehicle group as comparison. * $p < 0.05$, indicates a significant difference from the vehicle group on that test point



showed little effect on pup licking. The effects of amisulpiride, when compared to the other atypical or typical APDs, were delayed in onset and prolonged in duration. Aripiprazole, on the other hand, displayed no detrimental effect on two major components of maternal behavior, pup retrieval, and pup licking, but produced a paradoxical enhancement on pup nursing. In the following sections, we discuss these results, their likely mechanisms, some clinical implications, and the limitations of this work.

The disruptive effects of the high dose of amisulpiride (100 mg/kg) on active components of maternal behavior (pup retrieval and nest building) resemble those of other APDs. It has been shown that acutely administered typical APDs, such as haloperidol and pimozide, as well as atypical APDs, clozapine, risperidone, quetiapine, and olanzapine disrupt pup retrieval, pup licking, and nest building (Giordano et al. 1990; Hansen et al. 1991; Li et al. 2004, 2005; Silva et al. 2001; Stern and Keer 1999; Stern and Taylor 1991). These effects are probably due to blockade of postsynaptic dopamine D_2 receptors because this is the only common property shared by all these antipsychotics

(Kapur and Mamo 2003). Consistent with this view, in an ongoing study we have observed that amisulpiride induced a high dopamine D_2 receptor occupancy (>80%) in the striatum (dorsolateral + accumbens combined) in rats treated with 100 mg/kg amisulpiride and sacrificed 6 h after injections (unpublished observations). It has been shown that haloperidol, *cis*-flupenthixol, and pimozide selectively microinfused into the nucleus accumbens produce the same pattern of disruption in pup retrieval, pup licking, and nest building as are observed after systemic administration (Keer and Stern 1999; Li 2002; Silva et al. 2003). Thus, it is likely that the effects of amisulpiride observed here reflect a disruption of dopamine transmission in mesolimbic accumbens D_2/D_3 receptors, thereby disrupting the ability of the accumbens to act as a transducer of motivational commands into action (Mogenson et al. 1980).

Amisulpiride, as an atypical antipsychotic, did show some unique dose and time effects on maternal behavior in comparison to other atypicals. Whereas at the high dose (100 mg/kg) amisulpiride did not significantly impact pup licking (marginally decreased it), at lower doses (10 and

30 mg/kg) it significantly enhanced pup licking. The enhancement of pup licking is unique because none of the APDs that have been previously tested in this model show such an effect. It is not clear what the underlying neurochemical mechanism for this effect might be. At low doses (≤ 10 mg/kg), amisulpiride is found to preferentially block presynaptic dopamine autoreceptors that control dopamine synthesis and release in the rat, whereas at higher doses (40–80 mg/kg), it primarily blocks postsynaptic dopamine D_2 receptors and possesses characteristics found in classical neuroleptics such as haloperidol (Schoemaker et al. 1997). Therefore, it is likely that the enhancement in pup licking at 10 and 30 mg/kg is due to its antagonist action on presynaptic dopamine autoreceptors, perhaps leading to an increase in dopamine transmission resulting from a disinhibition of dopamine release. In agreement with this idea are recent findings showing that the dopamine level (as monitored using *in vivo* voltammetry) increased significantly with pup licking, and the magnitude and duration of the increase in the dopamine level were significantly correlated with the duration of the licking bout (Champagne et al. 2004). Increasing dopamine levels by injecting the selective dopamine uptake inhibitor GBR 12909 also increased pup licking in low-licking mothers (Champagne et al. 2004). Thus, it is quite possible that the ability of amisulpiride to enhance dopamine transmission at low doses (which has been postulated to explain its efficacy against negative symptoms) may be a factor here. The disruptive effects of amisulpiride on pup retrieval and nest building at the high dose and its enhancement effect on pup licking at lower doses are both consistent with data in humans, which shows a similar dose-dependent biphasic action for this drug. Amisulpiride has been shown to have selective efficacy for negative symptoms of schizophrenia at low doses (e.g., 50–100 mg/day, mostly <300 mg/day) and efficacy for positive symptoms only at higher doses (>400 mg/day) (Boyer et al. 1995; Delcker et al. 1990). The former effect is thought to be due to enhanced dopamine release at presynaptic sites, whereas the latter effect is thought to be due to a blockade of dopamine receptors at the postsynaptic level (Scatton et al. 1997).

Amisulpiride was also unique in that the effects were delayed in onset and lasted for a relatively long period. Amisulpiride-induced disruptions in pup retrieval and nest building were still apparent even 24 h after injection. This feature further distinguishes amisulpiride from other atypical APDs. Li et al. (2004) found that clozapine, risperidone, and quetiapine show transient and short-lasting effects (onset within 30 min and no residue at 6 h) on pup retrieval, pup licking, and nest building. In the present study, aripiprazole, another atypical antipsychotic, also showed a similar transient effect. The prolonged action of amisulpiride has been reported in other animal studies. For example, Protais et al. (1985) found that the ability of amisulpiride to antagonize apomorphine-induced climbing was still apparent when the drug was injected systemically 240 min before testing or centrally 120 min before testing. Unpublished data from our laboratory have shown that

amisulpiride can disrupt two-way conditioned avoidance responding even at the 24-h postinjection testing point. This long-lasting effect is probably due to the limited ability for amisulpiride to cross the blood–brain barrier and its negligible metabolism. Amisulpiride is one of the most hydrophilic antipsychotics and has difficulty permeating the blood–brain barrier (Hartter et al. 2003), entering the CNS via a slower and less efficient mechanism through the choroid plexus. Its elimination from the body is mainly accomplished by renal clearance, which is a slow process because it is substantially reabsorbed from the distal portion of the nephron. Thus, even at 24 h postinjection, the drug level in the brain may still be high enough to affect behavioral functions.

Aripiprazole is the only antipsychotic drug that we know of that does not show any detrimental effect on pup retrieval, pup licking, or pup nursing. It only inhibited nest building, which according to our previous observation (Li et al. 2004, 2005), is the component of rat maternal behavior most vulnerable to pharmacological disturbance. For example, haloperidol (0.2 mg/kg) disrupted nest building at the 24-h point when it had lost its effects on other components of maternal behavior. On the other hand, it significantly enhanced pup nursing. Both effects were short-lasting, peaked at 1 or 2 h after drug administration, and disappeared at 4 h postinjection.

The first thing to consider is whether the lack of effect of aripiprazole on pup retrieval and pup licking is due to insufficient dosing. This explanation seems unlikely for several reasons. First, aripiprazole at 10 and 30 mg/kg significantly disrupts conditioned avoidance response (Hertel et al. 2005; Reckless et al. 2005), a reliable indicator of antipsychotic-relevant activity in animals (Wadenberg and Hicks 1999). All other APDs that we have tested so far at the doses that cause disruptions on conditioned avoidance also disrupt active components of maternal behavior. Secondly, aripiprazole at the doses used here induces $>85\%$ D_2 occupancies in rodents (Reckless et al. 2005), a level that is commonly found in human volunteers treated with adequate doses of aripiprazole (Yokoi et al. 2002). Thus, it seems likely that the doses we used were sufficient and clinically relevant, and the lack of effect of aripiprazole on pup retrieval and pup licking may reflect an intrinsic feature of this drug.

This intrinsic feature may be related to its novel mechanism of action. Whereas all other available APDs are antagonists of dopamine D_2 receptors, aripiprazole is a high-affinity partial D_2 agonist with modest intrinsic efficacy. The partial agonist property has been demonstrated in biochemical and behavioral studies conducted *in vitro* (Burris et al. 2002; Lawler et al. 1999) and *in vivo* (Hirose et al. 2004; Kikuchi et al. 1995). For example, one piece of evidence for its agonist activity is its ability to inhibit the spontaneous firing of dopamine neurons when applied locally to the ventral tegmental area (Momiya et al. 1996), and its antagonist activity is evidenced by its inhibitory effects on apomorphine- and amphetamine-induced hyperlocomotion (Kikuchi et al. 1995). Its partial D_2 agonist property is also shown in human imaging stud-

ies. In most clinical studies, antipsychotic action emerges when antipsychotics block about 60–65% dopamine D₂ receptors, and motor side effects appear when blockade goes beyond 80%. In the case of aripiprazole, it can occupy up to 95% of striatal D₂-like dopamine receptors at clinical doses, but the incidence of extrapyramidal side effects is no higher than with placebo. Thus, aripiprazole may have spared pup retrieval and pup licking, two major components of maternal behavior, by generating a drug-induced dopamine-like signaling via its intrinsic efficacy, although it was blocking the receptors from stimulation by endogenous dopamine.

In addition to the action of aripiprazole on dopamine receptors, this drug shows partial agonism at 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors (Jordan et al. 2002; Kikuchi et al. 1995). Thus, it is conceivable that the actions of aripiprazole at 5-HT_{1A} and 5-HT_{2A} receptors may also contribute to the lack of effect on pup retrieval and pup licking. However, this explanation seems less likely because (1) other atypicals such as clozapine, risperidone, quetiapine, and olanzapine all have the antagonist affinity to 5-HT_{2A} receptors; however, they all show disruptive effects on pup retrieval and pup licking; (2) the serotonin systems, in general, have not been found to be critical for maternal behavior (Brunner et al. 1999; Lonstein et al. 2003). Prepartum and postpartum depletions of 5-HT were without effect on maternal behavior per se but might affect the expression of this behavior by interfering with suckling-induced prolactin release (Barofsky and Harney 1978; Barofsky et al. 1983; Rowland et al. 1978).

The present study is probably the first to emphasize the effects of amisulpiride and aripiprazole on a complex social behavior. We are also not aware of any studies that have examined the effects of these drugs on other types of social behaviors (e.g., social interaction, sexual behavior). Certainly, most typical and atypical APDs generally display a disruptive effect on social interaction and active sexual behaviors (Hansen et al. 1981; Holloway and Thor 1985; Li et al. 2001; Pfaus and Phillips 1989, 1991), which parallels the effects of these drugs on maternal behaviors (Li et al. 2004, 2005). These findings, along with our present data, are consistent with clinical observations showing that antipsychotics interfere with human maternal behavior and sexual function (Fleischhacker et al. 1994; Hummer et al. 1999) and suggest that the disruptive effects of these APDs on maternal behavior may represent an unwanted side effect, bearing some similarities to the neuroleptic-induced deficit syndrome (NIDS) (Awad 1993; Awad and Hogan 1994). In this regard, both amisulpiride and aripiprazole show some favorable characteristics over other antipsychotics. Amisulpiride displays its uniqueness in its favorable effects on pup licking at low doses, whereas aripiprazole shows its uniqueness in its lack of disruptions on pup retrieval and pup licking. These data provide some impetus to examine if these characteristics translate into better subjective tolerability of these drugs from the patient's perspective.

Our work is also relevant to understanding why schizophrenic patients exhibit poor quality of maternal care

(Bosanac et al. 2003). Schizophrenic mothers, in general, show less positive emotional responses and less social contact with their infants than do healthy mothers (McNeil et al. 1985; Naslund et al. 1985; Persson-Blennow et al. 1984, 1986). They are more remote, silent, and insensitive during mother–infant play (Riordan et al. 1999; Snellen et al. 1999). Most studies on the issue of the schizophrenic mother–infant relationship have focused on the influence from the illness itself, with little or no reference to the possible effects of antipsychotic medication (Bosanac et al. 2003; Riordan et al. 1999; Snellen et al. 1999). Our work suggests that antipsychotic medication might also contribute to the observed poor quality of maternal care in schizophrenic mothers. The challenge that lies ahead is how to distinguish the disruptive effects of the schizophrenic symptoms (positive and negative) from those of medications.

Finally, we should point out some limitations of this work. In this study, we used a repeated testing design in which each subject was tested six to seven times. Although necessary for identifying the time course of drug action, this design entails at least two problems. One is that the effects observed at the later time points may not reflect the sole pharmacological action of the drug but may arise from an interaction between the drug and repeated testing. Animals that are repeatedly tested under antipsychotics across similar situations (e.g., catalepsy, conditioned avoidance, and treadmill locomotion), show a response to drug treatment that tends to increase in magnitude and prolong in duration (Beninger et al. 1983; Hillegaart et al. 1987). Another problem is that since the tests were not equally spaced (the early tests were separated by 30 min and the later tests by 2 h), the uneven distribution of testing may influence the mother rats differently and may cause them to display different patterns of maternal behavior. Although we cannot rule out these effects, the inclusion of the vehicle group and the return of behavior to normalcy at the end of the testing mitigates against these confounds.

Acknowledgements This study was funded by an Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression (NARSAD) to Dr. Shitij Kapur, by an Ontario Mental Health Foundation postdoctoral fellowship to Dr. Ming Li, and by Natural Sciences and Engineering Research Council (NSERC) to Dr. Alison Fleming. We thank Dr. Sridhar Natesan for his insightful discussion and technical assistance on drug dosing. We also thank Dr. Robert Featherstone for his comments on an early draft of this manuscript. The constructive comments of two anonymous reviewers were greatly appreciated.

References

- Aihara K, Shimada J, Miwa T, Tottori K, Burris KD, Yocca FD, Horie M, Kikuchi T (2004) The novel antipsychotic aripiprazole is a partial agonist at short and long isoforms of D2 receptors linked to the regulation of adenylyl cyclase activity and prolactin release. *Brain Res* 1003:9–17
- Awad AG (1993) Subjective response to neuroleptics in schizophrenia. *Schizophr Bull* 19:609–618

- Awad AG, Hogan TP (1994) Subjective response to neuroleptics and the quality of life: implications for treatment outcome. *Acta Psychiatr Scand Suppl* 380:27–32
- Barofsky AL, Harney JW (1978) Impairments in lactation in the rat following destruction of the median raphe nucleus. *Neuroendocrinology* 26:333–351
- Barofsky AL, Taylor J, Massari VJ (1983) Dorsal raphe-hypothalamic projections provide the stimulatory serotonergic input to suckling-induced prolactin release. *Endocrinology* 113:1894–1903
- Beninger RJ, Phillips AG, Fibiger HC (1983) Prior training and intermittent retraining attenuate pimozide-induced avoidance deficits. *Pharmacol Biochem Behav* 18:619–624
- Bosanac P, Buist A, Burrows G (2003) Motherhood and schizophrenic illnesses: a review of the literature. *Aust N Z J Psychiatry* 37:24–30
- Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F (1995) Treatment of negative symptoms in schizophrenia with amisulpiride. *Br J Psychiatry* 166:68–72
- Brunner D, Buhot MC, Hen R, Hofer M (1999) Anxiety, motor activation, and maternal–infant interactions in 5HT1B knockout mice. *Behav Neurosci* 113:587–601
- Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, Yocca FD, Molinoff PB (2002) Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* 302:381–389
- Champagne FA, Chretien P, Stevenson CW, Zhang TY, Gratton A, Meaney MJ (2004) Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. *J Neurosci* 24:4113–4123
- Delcker A, Schoon ML, Oczkowski B, Gaertner HJ (1990) amisulpiride versus haloperidol in treatment of schizophrenic patients—results of a double-blind study. *Pharmacopsychiatry* 23:125–130
- Duarte C, Biala G, Le Bihan C, Hamon M, Thiebot MH (2003) Respective roles of dopamine D2 and D3 receptors in food-seeking behaviour in rats. *Psychopharmacology (Berl)* 166:19–32
- Fleischhacker WW, Meise U, Gunther V, Kurz M (1994) Compliance with antipsychotic drug treatment: influence of side effects. *Acta Psychiatr Scand Suppl* 382:11–15
- Fujikawa M, Nagashima M, Inoue T, Yamada K, Furukawa T (1996) Partial agonistic effects of OPC-14597, a potential antipsychotic agent, on yawning behavior in rats. *Pharmacol Biochem Behav* 53:903–909
- Giordano AL, Johnson AE, Rosenblatt JS (1990) Haloperidol-induced disruption of retrieval behavior and reversal with apomorphine in lactating rats. *Physiol Behav* 48:211–214
- Goudie A, Taylor A (1998) Comparative characterisation of the discriminative stimulus properties of clozapine and other antipsychotics in rats. *Psychopharmacology (Berl)* 135:392–400
- Gupta S, Masand P (2004) Aripiprazole: review of its pharmacology and therapeutic use in psychiatric disorders. *Ann Clin Psychiatry* 16:155–166
- Hansen S, Stanfield EJ, Everitt BJ (1981) The effects of lesions of lateral tegmental noradrenergic neurons on components of sexual behavior and pseudopregnancy in female rats. *Neuroscience* 6:1105–1117
- Hansen S, Harthorn C, Wallin E, Lofberg L, Svensson K (1991) Mesotelencephalic dopamine system and reproductive behavior in the female rat: effects of ventral tegmental 6-hydroxydopamine lesions on maternal and sexual responsiveness. *Behav Neurosci* 105:588–598
- Hartert S, Huwel S, Lohmann T, Abou El Ela A, Langguth P, Hiemke C, Galla HJ (2003) How does the benzamide antipsychotic amisulpiride get into the brain?—An in vitro approach comparing amisulpiride with clozapine. *Neuropsychopharmacology* 28:1916–1922
- Hertel P, Olsen CK, Didriksen M, Arnt J, Marquis K, van der Heyden J, McCreary A, Hesselink MB (2005) Bifeprunox: a new and different antipsychotic. *Schizophr Bull* 31:301
- Hillegaart V, Ahlenius S, Magnusson O, Fowler CJ (1987) Repeated testing of rats markedly enhances the duration of effects induced by haloperidol on treadmill locomotion, catalepsy, and a conditioned avoidance response. *Pharmacol Biochem Behav* 27:159–164
- Hirose T, Uwahodo Y, Yamada S, Miwa T, Kikuchi T, Kitagawa H, Burris KD, Altar CA, Nabeshima T (2004) Mechanism of action of aripiprazole predicts clinical efficacy and a favourable side-effect profile. *J Psychopharmacol* 18:375–383
- Holloway WR Jr, Thor DH (1985) Interactive effects of caffeine, 2-chloroadenosine and haloperidol on activity, social investigation and play fighting of juvenile rats. *Pharmacol Biochem Behav* 22:421–426
- Hummer M, Kemmler G, Kurz M, Kurzthaler I, Oberbauer H, Fleischhacker WW (1999) Sexual disturbances during clozapine and haloperidol treatment for schizophrenia. *Am J Psychiatry* 156:631–633
- Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA (2002) The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. *Eur J Pharmacol* 441:137–140
- Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, Ali MW (2002) Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 63:763–771
- Kapur S, Mamo D (2003) Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry* 27:1081–1090
- Kapur S, Remington G (2001) Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. *Annu Rev Med* 52:503–517
- Kapur S, Wadenberg ML, Remington G (2000) Are animal studies of antipsychotics appropriately dosed? Lessons from the bedside to the bench. *Can J Psychiatry* 45:241–246
- Kapur S, VanderSpek SC, Brownlee BA, Nobrega J (2003) Antipsychotic dosing in preclinical models is often unrepresentative of the clinical condition: a suggested solution based on in vivo occupancy. *J Pharmacol Exp Ther* 305:1–7
- Keer SE, Stern JM (1999) Dopamine receptor blockade in the nucleus accumbens inhibits maternal retrieval and licking, but enhances nursing behavior in lactating rats. *Physiol Behav* 67:659–669
- Kikuchi T, Tottori K, Uwahodo Y, Hirose T, Miwa T, Oshiro Y, Morita S (1995) 7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity. *J Pharmacol Exp Ther* 274:329–336
- Lawler CP, Prioleau C, Lewis MM, Mak C, Jiang D, Schetz JA, Gonzalez AM, Sibley DR, Mailman RB (1999) Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* 20:612–627
- Li M (2002) Differential involvement of nucleus accumbens shell and core subregions in maternal performance and maternal memory in female rats. Department of Psychology, University of Toronto, Toronto
- Li M, Kapur S, Fleming A (2001) Antipsychotics interfere with maternal and social behaviors in rats: differential effects of haloperidol and clozapine. *Schizophr Res* 49:93
- Li M, Davidson P, Budin R, Kapur S, Fleming AS (2004) Effects of typical and atypical antipsychotic drugs on maternal behavior in postpartum female rats. *Schizophr Res* 70:69–80
- Li M, Budin R, Fleming A, Kapur S (2005) Effects of chronic typical and atypical antipsychotic drug treatment on maternal behavior in rats. *Schizophr Res* 75:325–336
- Lonstein JS, Dominguez JM, Putnam SK, De Vries GJ, Hull EM (2003) Intracellular preoptic and striatal monoamines in pregnant and lactating rats: possible role in maternal behavior. *Brain Res* 970:149–158

- McNeil TF, Naslund B, Persson-Blennow I, Kaij L (1985) Offspring of women with nonorganic psychosis: mother–infant interaction at three-and-a-half and six months of age. *Acta Psychiatr Scand* 71:551–558
- Meltzer HY, Li Z, Kaneda Y, Ichikawa J (2003) Serotonin receptors: their key role in drugs to treat schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 27:1159–1172
- Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14:69–97
- Moller HJ (2003) amisulpride: limbic specificity and the mechanism of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry* 27:1101–1111
- Momiyama T, Amano T, Todo N, Sasa M (1996) Inhibition by a putative antipsychotic quinolinone derivative (OPC-14597) of dopaminergic neurons in the ventral tegmental area. *Eur J Pharmacol* 310:1–8
- Naber D, Lambert M (2004) Aripiprazole: a new atypical antipsychotic with a different pharmacological mechanism. *Prog Neuropsychopharmacol Biol Psychiatry* 28:1213–1219
- Nakai S, Hirose T, Uwahodo Y, Imaoka T, Okazaki H, Miwa T, Nakai M, Yamada S, Dunn B, Burris KD, Molinoff PB, Tottori K, Altar CA, Kikuchi T (2003) Diminished catalepsy and dopamine metabolism distinguish aripiprazole from haloperidol or risperidone. *Eur J Pharmacol* 472:89–97
- Naslund B, Persson-Blennow I, McNeil TF, Kaij L (1985) Offspring of women with nonorganic psychosis: mother–infant interaction at three and six weeks of age. *Acta Psychiatr Scand* 71:441–450
- Perrault G, Depoortere R, Morel E, Sanger DJ, Scatton B (1997) Psychopharmacological profile of amisulpride: an antipsychotic drug with presynaptic D2/D3 dopamine receptor antagonist activity and limbic selectivity. *J Pharmacol Exp Ther* 280:73–82
- Persson-Blennow I, Naslund B, McNeil TF, Kaij L, Malmquist-Larsson A (1984) Offspring of women with nonorganic psychosis: mother–infant interaction at three days of age. *Acta Psychiatr Scand* 70:149–159
- Persson-Blennow I, Naslund B, McNeil TF, Kaij L (1986) Offspring of women with nonorganic psychosis: mother–infant interaction at one year of age. *Acta Psychiatr Scand* 73:207–213
- Pfaus JG, Phillips AG (1989) Differential effects of dopamine receptor antagonists on the sexual behavior of male rats. *Psychopharmacology (Berl)* 98:363–368
- Pfaus JG, Phillips AG (1991) Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. *Behav Neurosci* 105:727–743
- Protais P, Hermier C, Costentin J (1985) The discriminant dopamine antagonist property of benzamides is observed at various times after their systemic or intracerebroventricular administration. *Neuropharmacology* 24:861–867
- Reckless G, Natesan S, Parkes J, VanderSpek S, Nobrega J, Kapur S (2005) Dissociation between blockade and functional antagonism of D2 receptors—comparing aripiprazole to other typical and atypical antipsychotics in animal models. *Schizophr Bull* 31:309
- Riordan D, Appleby L, Faragher B (1999) Mother–infant interaction in post-partum women with schizophrenia and affective disorders. *Psychol Med* 29:991–995
- Rowland D, Steele M, Moltz H (1978) Serotonergic mediation of the suckling-induced release of prolactin in the lactating rat. *Neuroendocrinology* 26:8–14
- Scatton B, Claustre Y, Cudennec A, Oblin A, Perrault G, Sanger DJ, Schoemaker H (1997) amisulpride: from animal pharmacology to therapeutic action. *Int Clin Psychopharmacol* 12(Suppl 2): S29–S36
- Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, Curet O, Oblin A, Gonon F, Carter C, Benavides J, Scatton B (1997) Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. *J Pharmacol Exp Ther* 280:83–97
- Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R (2003) Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 28:1400–1411
- Silva MR, Bernardi MM, Felicio LF (2001) Effects of dopamine receptor antagonists on ongoing maternal behavior in rats. *Pharmacol Biochem Behav* 68:461–468
- Silva MR, Bernardi MM, Cruz-Casallas PE, Felicio LF (2003) Pimozide injections into the nucleus accumbens disrupt maternal behaviour in lactating rats. *Pharmacol Toxicol* 93:42–47
- Snellen M, Mack K, Trauer T (1999) Schizophrenia, mental state, and mother–infant interaction: examining the relationship. *Aust N Z J Psychiatry* 33:902–911
- Stern JM, Keer SE (1999) Maternal motivation of lactating rats is disrupted by low dosages of haloperidol. *Behav Brain Res* 99:231–239
- Stern JM, Taylor LA (1991) Haloperidol inhibits maternal retrieval and licking, but facilitates nursing behavior and milk ejection in lactating rats. *J Neuroendocrinol* 3:591–596
- Wadenberg ML, Hicks PB (1999) The conditioned avoidance response test re-evaluated: is it a sensitive test for the detection of potentially atypical antipsychotics? *Neurosci Biobehav Rev* 23:851–862
- Wadenberg ML, Kapur S, Soliman A, Jones C, Vaccarino F (2000) Dopamine D2 receptor occupancy predicts catalepsy and the suppression of conditioned avoidance response behavior in rats. *Psychopharmacology (Berl)* 150:422–429
- Yokoi F, Grunder G, Biziere K, Stephane M, Dogan AS, Dannals RF, Ravert H, Suri A, Bramer S, Wong DF (2002) Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomography and [¹¹C]raclopride. *Neuropsychopharmacology* 27:248–259