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Antipsychotic Drugs on Maternal Behavior in Rats

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Abstract

Rat maternal behavior is a complex social behavior. Many clinically used antipsychotic drugs, including the typical drug haloperidol and atypical drugs clozapine, risperidone, olanzapine, quetiapine, aripiprazole and amisulpride, all disrupt active maternal responses (e.g. pup retrieval, pup licking and nest building) to various extents. In this review, I present a summary of recent studies on the behavioral effects and neurobiological mechanisms of antipsychotic action on maternal behavior in rats. I argue that antipsychotic drugs at the clinical relevant doses disrupt active maternal responses primarily by suppressing maternal motivation. Atypical drug-induced sedation also contributes to their disruptive effects, especially that on pup nursing. Among many potential receptor mechanisms, dopamine D_2 receptors and serotonin 5-$HT_{2A/2C}$ receptors are shown to be critically involved in the mediation of the maternal disruptive effects of antipsychotic drugs, with D_2 receptors contributing more to typical antipsychotic-induced disruptions, while 5-$HT_{2A/2C}$ receptors contributing more to atypical drug-induced disruption. The nucleus accumbens shell-related reward circuitry is an essential neural network in the mediation of the behavioral effects of antipsychotic drugs on maternal behavior. This research not only helps to understand the extent and mechanisms of impacts of antipsychotic medications on human maternal care, but also is important for enhancing our understanding of the neurochemical basis of maternal behavior. It is also valuable for understanding the complete spectrum of therapeutic and side-effects of antipsychotic treatment. This knowledge may facilitate the development of effective intervening strategies to help patients coping with such undesirable effects.

Keywords

maternal behavior; antipsychotic drugs; dopamine D_2 receptor; serotonin 5-$HT_{2A/2C}$ receptor; nucleus accumbens; prefrontal cortex; rat

Introduction

Maternal behavior in rats is a highly motivated and well-organized social behavior. It is naturally expressed for the first time with the birth of the first litter. Within hours of parturition, the mother rat reconstructs the nest, retrieves the displaced pups, gathers them together in the nest site and adopts a nursing posture over the pups to permit suckling (Rosenblatt and Lehrman, 1963; Dollinger *et al.*, 1980). The mother rat (dam) continues to exhibit the full repertoire of maternal behavior (pup-licking, pup retrieval, nest-building and

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nursing) over the subsequent 2–3 week period, although as the pups mature, the intensity and quality of her behavior changes (Rosenblatt and Lehrman, 1963; Galef, 1981). Each component of maternal behavior, although distinct in appearance and motoric requirements, is synchronized seamlessly to ensure the well-being of the young. Psychologically, the dams are shown to be less anxious, more attentive to pups or pup-related cues, highly motivated to retrieve and protect pups and possessing altered learning and memory ability (Lee *et al.*, 2000; Lonstein, 2007; Kinsley and Lambert, 2008). Thus the successful expression and maintenance of maternal behavior require multiple psychological processes working together synergistically.

Maternal behavior is an ecologically valid and complex behavior system that cuts across mammalian species and shares many direct features with human mothering behaviors (Fleming and Corter, 1988; Rosenblatt, 1989). It is thus a useful model for the study of complex behavioral effects and neurobiological mechanisms of psychoactive drugs in a social domain. Investigation of the antipsychotic treatment effects on maternal behavior in rats represents this aspect of neuropsychopharmacological research.

Antipsychotic drugs (APDs) represent a class of psychoactive drugs that are used to treat schizophrenia and other neuropsychiatric disorders (e.g. autism, bipolar disorder, Tourette's syndrome, etc.). Currently they are classified into two groups, typical (or first generation) and atypical (or second generation) based on their impacts on prolactin and extrapyramidal motor syndromes (EPS) (Kapur and Seeman, 2001), with atypical drugs offering reduced risk of EPS and prolactin elevation. Some studies suggest that atypical APDs show superior efficacy in improving negative symptoms of schizophrenia (e.g., apathy, lack of motivation, and lack of interpersonal and social drive/interaction) (Marder and Meibach, 1994) and cognitive impairments (Purdon *et al.*, 2000). However, overall the evidence of this superiority has been neither consistent nor robust (Leucht *et al.*, 1999; Lieberman *et al.*, 2005). It is safe to say that all APDs share a common feature in improving the psychotic symptoms of schizophrenia and preventing their recurrence.

In this review, I will present a summary of recent studies from our laboratory on the behavioral effects and neurobiological mechanisms of antipsychotic action on maternal behavior in rats. Research in this field generally has three purposes in mind. From a behavioral neuroscience perspective, studying the effects of antipsychotic treatment on rodent maternal behavior will enhance our understanding of the neurochemical basis of maternal behavior and the altered psychological processes. Antipsychotic drugs are chemical compounds that target dopamine, serotonin and other neurotransmitter systems, notably dopamine D_2, serotonin 5-HT_{2A}, and/or 5-HT_{1A} receptors. Thus, antipsychotic drugs can be used as pharmacological tools to identify the neuroreceptor mechanisms underlying maternal behavior. For example, previous research has shown that dopamine D_2 receptor is important for maternal motivation (Wegener *et al.*, 1988; Giordano *et al.*, 1990; Stern and Taylor, 1991; Silva *et al.*, 2001), while the serotonin 5-HT_{2A} and 5-HT_{2C} receptors are required for the normal expression of maternal performance (Chen *et al.*, 2014). From a psychopharmacology perspective, understanding the effects of antipsychotic action on maternal behavior is valuable for the understanding of the complete spectrum of therapeutic and side-effects of antipsychotic treatment. Many commonly used animal tests of

antipsychotic drugs, such as conditioned avoidance responses, prepulse inhibition of acoustic startle or latent inhibition, are simple and have a high predictive validity, yet, they are ethologically artificial mechanistic behaviors and may not reflect well the complex and multi-dimensional actions of APDs on affective, cognitive and social functions. Thus, the study of antipsychotic effects on maternal behavior, a complex and natural social behavior, with its onset and expression clearly supported by the coordination and interaction among multiple psychological functions (e.g. sensorimotor ability, emotion regulation and motivation) would deepen and broaden our understanding of behavioral effects of antipsychotic drugs. From a clinical pharmacology perspective, studying the behavioral effects of APDs on maternal behavior may have a direct and immediate implication, since more than half of the women with schizophrenia in the United States are also mothers (Seeman, 2004). Studies on the mother-child relationship reveal that the quality of maternal care from mothers with schizophrenia is generally inferior to that from healthy mothers. One contributing factor recognized by both patients and their clinicians is antipsychotic medications. However, it is not clear to what extent antipsychotic drugs impact the quality of maternal care and through what psychological and neurobiological mechanisms. With the new generation of APDs, which do not produce sustained hyperprolactinemia, there has been an increasing trend of schizophrenic women becoming first-time mothers. Understanding the antipsychotic effects on maternal behavior in mother rats, especially in those animal models of postpartum schizophrenia, would help us understand the extent and mechanisms of impacts of antipsychotic medications on human maternal care. This knowledge may facilitate the development of effective behavioral or other intervening strategies to help patients coping with such undesirable effects. Given that the quality of maternal care has long-lasting cognitive, emotional, behavioral, and social consequences for child development, and mothers with schizophrenia have to rely on medications chronically, it is clinically significant to know definitively and precisely the impact of antipsychotic drugs on the quality of maternal care.

In this review, I will first describe the basic behavioral effects of antipsychotic treatment on maternal behavior in rats, then present studies aimed at revealing the neuroreceptor mechanisms and neuroanatomical basis of antipsychotic action in maternal behavior. Finally, I will discuss the clinical implications of such preclinical studies for the understanding of the quality of human maternal care in patients who are also treated with antipsychotic medications.

Basic behavioral effects of antipsychotic drugs on maternal behavior in rats

Studies in the early 90s aimed at elucidating the role of the dopamine system in maternal behavior showed that acutely administered typical antipsychotics, such as haloperidol and pimozide, disrupt pup retrieval, pup licking and nest building but not nursing, in postpartum female rats. For example, Giordano et al. (1990) found that haloperidol dose-dependently inhibited pup retrieval and nest building, but not nursing and pup licking. Hansen et al. (1991) showed that raclopride administered to postpartum female mothers also significantly inhibited pup retrieval but not nursing. A similar effect of haloperidol on pup retrieval was

reported by Stern and Taylor (1991). Animals under the influence of antipsychotics are slower to approach pups and retrieve fewer pups. They also spend less time licking their offspring and building the nest. Regarding the atypical antipsychotic drugs, Silva et al (2001) found that clozapine at an even lower dose (1.5 mg/kg) impaired nest building, but not pup retrieval.

In recent years, we conducted a series of experiments that extended these findings to several commonly used atypical drugs. We showed that clozapine, risperidone and quetiapine also disrupt active components of maternal behavior in a dose-dependent fashion (Li *et al.*, 2004). Our results indicate that clinically comparable doses of haloperidol, clozapine, risperidone, and quetiapine (based on the 50–80% striatal D_2 receptor occupancy and efficacy in disrupting the conditioned avoidance response) (Wadenberg *et al.*, 2000) show no qualitative or quantitative differences in their disruptions but display different temporal characteristics. Haloperidol causes a prolonged disruption (up to 6 h after injection), whereas clozapine, risperidone, and quetiapine induce an early onset but transient disruption (~2 h). We attributed this temporal difference to the distinct temporal binding profiles of the D_2 receptor binding between haloperidol and the other drugs (haloperidol having a tighter binding to the D_2 receptor and dissociating from it at a slower rate than atypical drugs), rather than some other fundamental differences (Meltzer *et al.*, 1989; Kapur and Seeman, 2000, 2001; Seeman, 2000). It has been shown that after an acute administration (in non-pregnant animals) haloperidol shows prolonged D_2-related therapeutic effects and side-effects, whereas the effects of clozapine/risperidone/quetiapine tend to be more transient (Kapur and Seeman, 2001). Additionally, we found that other atypical antipsychotics such as olanzapine, amisulpride and aripiprazole also exhibit a certain degree of inhibition of active maternal responses in a dose-dependent fashion (Li *et al.*, 2005b; Zhao and Li, 2012). Chronic treatment with haloperidol or olanzapine (another widely prescribed atypical antipsychotic drug) via mini-pumps or repeated daily injections also significantly inhibits rat active maternal responses (Li *et al.*, 2005a). It seems that the antipsychotic-induced inhibition of pup retrieval, pup licking, and nest building may be an inherent feature of all currently available antipsychotics.

In contrast to the consistent suppressive effects of these APDs on active maternal behavior, their effects on nursing behavior diverged. Haloperidol had no effects on nursing. This is consistent with previous studies that also show that haloperidol does not disrupt nursing behavior (Giordano *et al.*, 1990) and may even increase nursing duration (Stern and Taylor, 1991). However, clozapine, risperidone, olanzapine and quetiapine all showed an inhibitory effect on nursing behavior at some points during the tests.

So far, all work has been focused on the direct effect of antipsychotic treatment on the behaviors of mothers. In a recent study we examined the effect of antipsychotic treatment to mother rats on their offspring's ultrasonic vocalizations (USV) as an indirect way of assessing the impact of antipsychotic treatment on the quality of maternal care (Li *et al.*, 2011). Rat pups often emit USV centered around 40 kHz as a response to various stressors (e.g. isolation, shock, temperature change, etc.), and as an early communicative behavior between pup and mother (Shair, 2007). An isolated pup would increase its emission of USV when it is briefly reunited with its mother and separated again. This potentiated effect is

termed “maternal potentiation” of pup USV and is believed to reflect a filial bond that has been formed by the pup during the first weeks of life (Shair, 2007). We took advantage of the facts that rat pups often increase emission of USV in response to separation and re-separation from dams, and that the potentiation of pup USV after a brief contact with dams presumably reflects different maternal experience (Shair, 2007). Therefore, changes in pup USV may reveal the subtle negative impact of antipsychotic treatment on maternal behavior of mother rats. We hypothesized that pups of antipsychotic-treated mother rats would show an increase in USVs as a compensatory response to their lack of adequate maternal care. On postnatal days 10, 12 and 14, mother rats were injected subcutaneously with either clozapine, haloperidol or sterile water. Then pups were taken away from their dams and placed in individually in separate bowls and tested for USV for 3 minutes (the 1st test). After the 1st test, half of the littermates were returned to the dam for 4.5 minutes (termed “maternal”), whereas another half were returned to the bowls with a heating pad underneath (termed “control”). At the end of the 4.5 minutes, the pups were tested again for USV for 3 minutes (the 2nd test), after which, all pups were returned to their mothers. We found that initial maternal separation (1st test) induced pup USVs and re-separation (2nd test in the “maternal” condition) further enhanced the number of pup USVs, confirming the maternal potentiation effect). Clozapine increased pup USVs in pups that were briefly reunited with their dams between the two tests, while it had little effect in pups that were not reunited with their dams. This finding suggests that altered maternal behavior exhibited by clozapine-treated dams during the 4.5-minute reunion period contributed to an increase in the number of pup USVs. In contrast to the effect of clozapine, haloperidol did not seem to have a great impact on pup USV. Because clozapine differs from haloperidol on pup nursing (i.e. haloperidol increases pup nursing, whereas clozapine decreases it), we speculated that the most likely cause of the potentiating effect of clozapine on pup USV is its disruptive effect on pup nursing. Clozapine also antagonizes histamine H_1 receptors and/or adrenergic receptors and causes a severe sedation (Fleischhacker *et al.*, 1994), so the observed effect of clozapine on pup USVs could be attributed to drug-induced sedation and sedation-induced alteration of maternal behavior via actions on H_1 receptors and/or adrenergic receptors (see below for a further study on this issue). Thus, this pup USV study introduced an innovative approach to study the behavioral effects of antipsychotic medication on rat maternal behavior. This paradigm may also be valuable for examining the effects of other psychoactive drugs on the developmental trajectory of the young and allows us to investigate the neurobiological processes underlying the mother-infant interactions.

Behavioral mechanisms: motoric, motivational, or sedative effects?

Although the antipsychotic-induced disruption of rat active maternal behavior is clear and robust, its underlying behavioral mechanisms are not. Since maternal behavior has motivational as well as motor components, and given that antipsychotic drugs (at least the typical ones) are known to produce motivational and motoric impairments (Ikemoto and Panksepp, 1999; Salamone and Correa, 2002), it raises the question of whether this disruptive effect is motivational or simply motoric. In addition, because atypical drugs like clozapine also give rise to sedation due to their actions on histamine H_1 receptors and/or adrenergic receptors (Fleischhacker *et al.*, 1994), the atypical drug-induced disruption also

could be attributed to drug-induced sedation. Several findings suggest that the maternal disruptive effect of antipsychotic treatment is not just a motor deficit: First, postpartum mothers treated with even 0.2 mg/kg haloperidol are able to pick up food pellets and carry them back to the nest (Giordano *et al.*, 1990), suggesting that pup retrieval and nest building deficits are observed in the presence of other preserved motor and oral-manipulation behaviors (Giordano *et al.*, 1990). Second, in our hands and those of others, haloperidol at 0.1 mg/kg does not produce catalepsy (De Ryck *et al.*, 1982; Wadenberg *et al.*, 2000), but it did produce maternal deficits, suggesting that this measure is not merely another manifestation of catalepsy. Third, atypicals such as clozapine, risperidone and quetiapine are well known for their lack of effect on catalepsy, especially at the doses employed in our study (Kapur *et al.*, 2003). Fourth, Giordano, et al, (1990) and tour study both found that 0.2 mg/kg haloperidol impairs pup retrieval when there is little or no mother-pup separation before testing. However, when 0.2 mg/kg haloperidol treated rats are pup-deprived for 4 h before observation, they show quite normal pup retrieval (Stern & Taylor, 1991).

To directly address the motivational versus motoric issue, we employed a pup-separation technique (Zhao and Li, 2009c). Previous work shows that removing pups from dams for several hours (>3 h) prior to maternal tests can significantly increase a mother rat's maternal motivation and stimulate dopamine release in the ventral striatum of maternal rats (Hansen *et al.*, 1993; Hansen, 1994). Three to six hours of pup deprivation can completely restore the pup retrieval deficit induced by massive dopamine depletion (80%) in the ventral striatum region in postpartum female rats (Hansen, 1994). Therefore, we reasoned that if the antipsychotic-induced maternal behavior deficits are primarily motivational, we would expect to see that antipsychotic-treated rats under this manipulation show improved maternal performance compared to testing under the standard condition (no-pup separation). No such improvement was expected to be observed if the deficits are motoric. We showed that separation of the pups from their mothers for 4h before testing significantly shortened pup approach latency, enhanced pup licking activity, and stimulated nursing behavior. Since pup separation is shown to affect maternal motivation, this observation suggests that antipsychotic-induced maternal deficits are motivational. This notion is also consistent with other evidence showing that disruptions of the mesolimbic dopamine system generally cause a deficit in maternal motivation, but not maternal performance (Hansen *et al.*, 1991; Fleming *et al.*, 1994a; Hansen, 1994; Keer and Stern, 1999; Stern and Keer, 1999). For example, Stern and Keer (1999) observed that when a dam is fitted with a muzzle, she persistently attempts to make snout contact with pups by pushing them with the muzzle. Using the muzzle-pushing and handling as indices of maternal motivation, they found that 0.05 mg/kg of haloperidol, a dose too low to affect actual pup retrieval under their testing conditions, significantly reduced muzzle-pushing and actual contact with pups, although the latency to initiate these behaviors was not impaired, indicating that dopamine deficits specifically impaired motivation. Pereira and Ferreira (2006) also reported that haloperidol-induced maternal behavior deficits can be overcome by testing mother rats with 12 h-isolated pups (demanding pups), which presumably are more effective in activating mothers' maternal motivation to retrieve and lick pups (Pereira and Ferreira, 2006).

Recently, we investigated the validity of a novel pup-based repeated elevated plus maze task to detect maternal motivation and explored the motivational aspect of haloperidol treatment. Sprague-Dawley postpartum or nulliparous female rats were tested 4 times every other day on postpartum days 4, 6 and 8 in an elevated plus maze with 4 pups placed on each end of the two open arms. Each test lasted 10 min and each rat was tested at baseline, 30 min, 100 min or 240 min after an injection of sterile water (vehicle) or haloperidol. Under the vehicle condition, postpartum rats retrieved pups into the closed arms, entered the open arms and closed arms more and had a higher moving speed than nulliparous rats. Thus, besides the number of pup retrieval and number of arm entries, the moving speed appeared to be another sensitive measure of maternal motivation. Haloperidol treatment not only dose- and time-dependently decreased the number of pup retrieval, but also decreased the moving speed. This finding provides another indirect evidence suggesting that antipsychotic drugs such as haloperidol disrupt maternal behavior via the action on maternal motivation. This idea and above findings are also consistent with the motivational salience hypothesis of antipsychotic action espoused by Kapur's group (Kapur, 2003; Kapur *et al.*, 2005, 2006), which suggests that antipsychotic drugs have a general effect of suppressing incentive salience of stimuli (in this case, pups and pup-related cues).

To examine the extent to which antipsychotic drug-induced sedation contributes to the disruption of active maternal behavior, we employed a repeated-treatment schedule and compared the effect of antipsychotics with that of chlordiazepoxide, an anxiolytic drug with a sedative effect (File, 1984). It is well known that with repeated drug administration, the sedative effect of antipsychotics and anxiolytics is greatly diminished (Chesler and Salamone, 1996), and tolerance can be seen with only four injections (File, 1984; Sanger, 1985). In the meantime, antipsychotic efficacy is progressively enhanced with repeated drug administration (Agid *et al.*, 2003; Li *et al.*, 2007). If drug-induced sedation plays a role in disrupting active maternal behavior, we expected that the haloperidol- and clozapine-induced maternal behavior deficits will show an improvement with repeated drug treatment. If this disruptive effect mainly reflects the motivational effect (Li *et al.*, 2004), the haloperidol- and clozapine-induced deficits would persist and show a deterioration with repeated drug treatment. Our results show that repeated haloperidol treatment produces a progressively enhanced disruption of pup retrieval and nest building and an attenuated sedation. In contrast, clozapine shows a progressively diminished disruption of pup retrieval and a concomitantly diminished sedative effect. Based on these findings, we suggest that acute haloperidol and clozapine disrupt active maternal responses primarily by suppressing maternal motivation, and drug-induced sedation also contributes to this disruptive effect, especially with clozapine.

Neurochemical mechanisms: dopamine D_2 receptors and/or 5-$HT_{2A/2C}$?

For typical antipsychotics, it is generally assumed that they disrupt maternal behavior by blocking dopamine D_2 receptors because they are primarily dopamine D_2 antagonists (Seeman *et al.*, 1976; Dragunow *et al.*, 1990), and because apomorphine, a dopamine receptor agonist, can reverse the inhibitory effects of haloperidol (Giordano et al., 1990). Because atypical antipsychotics (e.g., clozapine, olanzapine) generally have multiple-receptor binding profiles (Meltzer *et al.*, 1989; Miyamoto *et al.*, 2005), it is hard to pinpoint

their exact neurochemical mechanisms. Most atypicals possess a much more potent antagonism on the 5-HT_{2A} receptor in addition to relatively weak antagonism on D_2 receptors (Meltzer *et al.*, 2003). It is thus possible that the disruptive effect of atypical drugs on maternal behavior could be attributed to their action on D_2 receptors alone (Kapur and Seeman, 2001) or to their dual actions on both 5-HT_{2A} and D_2 receptors (Meltzer *et al.*, 1989) or on other receptors such as D_1, H_1 and adrenergic receptors. Regarding the 5-HT_{2A} receptor, the main target of atypical antipsychotic drugs, limited evidence suggests that it is involved in maternal aggression, as DOI (2,5-dimethoxy-4-iodo-amphetamine, a preferential 5-HT_{2A} agonist) and quipazine (a 5-HT_{2A} receptor antagonist) both decreased maternal aggressive behavior (Olivier *et al.*, 1995). In our examination of the neurochemical mechanisms that mediate the disruptive effect of haloperidol and clozapine (Zhao and Li, 2009b), we treated postpartum rats with haloperidol or clozapine together with either vehicle (saline or water), quinpirole or DOI. Maternal behaviors were tested at different time points before and after drug administration. We examined which of these two agonists was able to reverse the disruptive effects induced by haloperidol and clozapine. We found that both doses of quinpirole significantly improved the haloperidol-induced deficits in pup retrieval, pup licking, and nest building. Haloperidol-treated rats pretreated with quinpirole showed more shortened pup approach and retrieval latency than those pretreated with vehicle, and they retrieved more pups than the vehicle controls. By contrast, DOI failed to improve the haloperidol-induced disruption of maternal behavior, suggesting that haloperidolacts through its blockade of $D_{2/3}$ receptors.

In contrast to its effects on haloperidol-induced maternal behavior deficits, quinpirole had little effect on the clozapine-induced disruption. It even exacerbated the clozapine-induced disruption of pup retrieval and nest building. Interestingly, pretreatment of DOI dose-dependently improved the clozapine-induced disruption of pup approach, pup retrieval, and pup licking, but not nest building and pup nursing. Therefore, for the first time, this study demonstrates an interesting double dissociation between dopamine and serotonin receptor mechanisms in the mediation of haloperidol (a typical antipsychotic)- and clozapine (an atypical antipsychotic)-induced maternal behavior deficits in postpartum rats. These data strongly suggest that the haloperidol-induced maternal deficits are primarily mediated by the blockade of $D_{2/3}$ dopamine receptors, whereas the clozapine-induced maternal deficits are primarily mediated by the blockade of 5-$HT_{2A/2C}$ receptors.

Given the known antagonistic interaction between dopamine D_2 and adenosine A_{2A} receptors in the nucleus accumbens (Chen *et al.*, 2001), Pereira (2011) hypothesized that antagonizing adenosine A_{2A} receptor would enhance D_2-mediated neurotransmission, which in turn, would reduce haloperidol-induced maternal disruption. They administered a selective adenosine A_{2A} receptor antagonist MSX-3 together with haloperidol to postpartum female rats and found that MSX-3 (0.25–2.0 mg/kg, I.p.) produced a dose-related attenuation of the haloperidol-induced behavioral deficits on pup retrieval, pup licking and nest building. The intermediate doses of MSX-3 (0.5 and 1.0 mg/kg) also reversed the increase in nursing behaviors induced by haloperidol. This finding is in support of the idea that haloperidol disrupts maternal behavior primarily through its action on dopamine D_2 receptor. It should be noted that because APDs all have unique receptor binding profiles and

act on multiple receptors (Miyamoto *et al.*, 2005), they could affect maternal behavior via other neurochemical mechanisms, such as D_1, D_3, D_4, 5-HT_{1A}, 5-HT_{2C}, 5-HT_6 or 5-HT_7, α_1, α_2, m_1, H_1, etc. Besides the neuroreceptors, antipsychotic drugs may also influence maternal behavior by affecting other biological processes, including actions on neurotrophic factor levels, neurogenesis, neuronal plasticity, mitochondrial biogenesis, cell energetics, and antioxidant defense enzymes (Lieberman *et al.*, 2008). At present, a complete picture of the neurochemical basis of antipsychotic effects on maternal behavior is still lacking.

Neuroanatomical basis of antipsychotic treatment effect on maternal behavior

The ability of antipsychotics to induce *c*-Fos expression (a protein product of immediate-early gene *c-fos*) in forebrain regions has become a widely used molecular tool for identifying drugs with potential antipsychotic activity and liability for producing extrapyramidal side effects (EPS) (Robertson and Fibiger, 1992; Robertson *et al.*, 1994; Mo *et al.*, 2005; Natesan *et al.*, 2006). For example, haloperidol and clozapine are shown to produce different induction patterns of *c-Fos* expression in the forebrain, with haloperidol increasing Fos-positive neurons in the dorsolateral striatum (DLSt), nucleus accumbens (NA), and lateral septal nucleus (LSN) and clozapine producing such effects in the NA, medial prefrontal cortex (mPFC), and LSN. More interestingly, maternal behavior itself also increases *c-Fos* expression in the NA and LSN, as well as in the medial preoptic area (MPOA) (Fleming *et al.*, 1994b; Numan *et al.*, 1998; Stack *et al.*, 2002), Please ask au to confirm this deletionthe hypothalamic nucleus that is critical for the onset and maintenance of maternal behavior (Numan and Insel, 2003). Importantly, the intensity of *c-Fos* expression in MPOA maternal neurons has been found to be closely tied to the actual performance of the behavior (Numan and Numan, 1994; 1995).

In attempt to delineate the neural circuitry that mediates the maternal-disruptive effects of haloperidol and clozapine, we used the *c-Fos* immunohistochemistry technique together with the pharmacological tools and behavioral observations (Zhao and Li, 2010). The traditional approach in this field has been to examine brain regions that show drug-induced increase in c-Fos expression. Although it is straightforward, this approach has two problems. The first is that it fails to connect a drug's behavioral effects with its neuronal effects. In a typical study, animals are injected with an antipsychotic drug in their home cages, and sacrificed 2 hours later for brain analysis. Animal behavior and behavioral effects of the drug treatment are generally ignored. This issue is further complicated by the fact that animal behavior itself can also induce brain changes as indexed by c-Fos expression. For example, maternal behavior can stimulate c-Fos expression in the MPOA, the ventral bed nucleus of the stria terminalis (vBST) and the NA (Fleming *et al.*, 1994b; Numan and Numan, 1994; Lonstein *et al.*, 1998). The second problem is that it does not take the neurochemical mechanisms of different antipsychotic drugs into consideration. As mentioned above, although both haloperidol and clozapine disrupt active maternal responses, they do so via blocking dopamine D_2 and 5-$HT_{2A/2C}$ receptors, respectively. Thus, although both drugs can induce similar changes in c-Fos expression in the same brain regions, they may do so through distinct receptor mechanisms. Simply relying on the drug-induced c-Fos expression does not guarantee a correct identification of receptor-mediated neuroanatomical basis of a drug action. With these considerations in mind, we divided

postpartum rats into nine groups using a full factorial design comprising 3 pretreatment conditions: saline, quinpirole or DOI × 3 antipsychotic conditions: sterile water, haloperidol or clozapine. On the drug test day (one day on either Postpartum Day 6, 7, or 8), all subjects were tested twice, with the first maternal behavior test starting at 30 min prior to the injections and the second test occurring at 120 min after injections. Quinpirole, DOI or vehicle was injected subcutaneously twice, with the first injection at 10 min before and the second at 50 min after the haloperidol, clozapine or vehicle injection, as was done in Zhao and Li (2009b). Two hours after drug administration, rats were sacrificed and their brains were removed and processed for FOS protein staining. The brain regions analyzed included the neural sites that were implicated in the action of antipsychotic drugs [e.g., mPFC, nucleus accumbence shell (NAs), nucleus accumbence core (NAc), DLSt, ventral part of lateral septal nucleus (LSv)], and/or in the regulation of maternal behavior [e.g., MPOA, vBST, medial amygdaloid nucleus (MeA) and NAs and NAc] (Li and Fleming, 2003a; b; Numan *et al.*, 2005). We considered a brain region to be part of the neural circuitry of haloperidol or clozapine only if it mets the following three criteria: (1) it shows sensitive c-Fos response to treatment with haloperidol or clozapine; (2) it shows sensitive c-Fos responses to the reversal effect of pretreatment with quinpirole on haloperidol or DOI on clozapine; and (3) it does shows little or no c-Fos response to the pretreatment with DOI on haloperidol or quinpirole on clozapine. This approach ensured that the brain regions identified are behaviorally and neurochemically relevant to the specific action of haloperidol and clozapine.

Behaviorally, we replicated our previous findings (Zhao and Li, 2009b). Both haloperidol and clozapine disrupted pup retrieval, pup licking and nest building, but not nursing. Pretreatment with quinpirole, but not DOI, reversed the haloperidol-induced disruptions; in contrast, pretreatment with DOI, but not quinpirole, reversed the clozapine-induced disruptions. Neuroanatomically, we found that seven brain regions showed a significant drug treatment effect on c-Fos expression. The only brain region that did not show any change was the MeA. In comparison to the vehicle treatment, haloperidol significantly increased c-Fos expression in the NAs and NAc, DLSt and LSv, whereas clozapine significantly increased c-Fos expression in the NAs, LSv, vBST and mPFC. Quinpirole alone significantly increased c-Fos expression in the mPFC and vBST, while it decreased c-Fos expression in the NAs and NAc. DOI alone also significantly increased c-Fos expression in the mPFC, NAs, NAc, MPOA and vBST. Pretreatment with quinpirole significantly reduced the haloperidol-induced c-Fos increase in the NAs, NAc, DLSt and LSv, but also reduced the clozapine-induced c-Fos increase in the NAs. In contrast, pretreatment with DOI reduced the clozapine-induced c-Fos increase in the NAs, but did not alter the clozapine-induced c-Fos increase in the mPFC, LSv and vBST. Pretreatment with DOI also significantly reduced the haloperidol-induced c-Fos increase in the NAs, NAc and DLSt.

Our further analysis which took the effects of quinpirole and DOI itself on c-Fos expression into consideration (e.g. quinpriole reduced, while DOI increased c-Fos expression in the NAs and NAc) indicates that pretreatment with quinpriole and DOI produced opposite patterns of c-Fos expression in the brain regions (e,g. NAs, NAc, LSv, or DLSt) where haloperidol and clozapine had an effect. These dissociated pretreatment patterns were

consistent with our findings that only pretreatment with quinpirole (but not DOI) can reverse the haloperidol-induced disruption, whereas only pretreatment of DOI (but not quinpirole) can reverse the clozapine-induced disruption (Zhao and Li, 2009a). Based on these results, we concluded that haloperidol disrupts active maternal behavior primarily by blocking dopamine D_2 receptors in the neural circuitry involved the nucleus accumbens, lateral septum, and dorsolateral striatum. In contrast, clozapine disrupts active maternal behavior mainly by blocking serotonin 5-$HT_{2A/2C}$ receptors in the nucleus accumbens shell.

Olanzapine is a widely prescribed atypical antipsychotic drug with a high antagonist action against serotonin 5-$HT_{2A/2C}$ receptors, in addition to its action on D_2 receptors (Bymaster et al., 1999a, b). Mechanistically, it shares the D_2 antagonism with haloperidol and clozapine, and 5-$HT_{2A/2C}$ antagonism with clozapine. Thus, it resides in the pharmacological space in between (or combined with) haloperidol and clozapine in terms of D_2 occupancy coupled with 5-$HT_{2A/2C}$ and other actions. Our previous work showed that both acute and chronic olanzapine treatments at a relatively high dose (7.5 mg/kg, sc) disrupt active components of maternal behavior (e.g., pup retrieval, pup licking and nest building) (Li *et al.*, 2005a). However, little is known about the neural basis of the effect of olanzapine. In order to further delineate its neural basis we first established a dose-dependent function of the disruptive effect of olanzapine on rat maternal behavior (Zhao and Li, 2012). On postpartum Days 6–8, Sprague-Dawley mother rats were acutely injected with sterile water or olanzapine (1.0–5.0 mg/kg, sc). Maternal behavior was tested 2 h later, after which rats were sacrificed and brain tissues were collected and analyzed using c-Fos immunocytochemistry. We found that acute olanzapine treatment dose-dependently disrupted various components of maternal behavior (e.g., pup retrieval, pup licking, nest building, crouching) and increased c-Fos immunoreactivity in the mPFC, NAs and NAc, DLSt, LSv, CeA and VTA, important brain areas generally implicated in incentive motivation and reward processing. In contrast, olanzapine treatment did not alter c-Fos in the medial preoptic nucleus (MPN), vBST and medial amygdala (MeA), the core brain areas directly involved in the mediation of rat maternal behavior. These findings suggest that, like haloperidol and clozapine, olanzapine disrupts rat maternal behavior primarily by suppressing incentive motivation and reward processing via its action on the mesocortical and mesolimbic dopamine systems, but not by disrupting the core processes involved in the mediation of maternal behavior in particular.

The notion that antipsychotic drugs disrupt maternal behavior primarily by suppressing incentive motivation and reward processing, via their actions on the mesocortical and mesolimbic dopamine systems, is also consistent with other studies. For example, Keer and Stern (1999) showed that *cis*-flupenthixol (a mixed DA D_1 and D_2 receptor antagonist) microinfused into the nucleus accumbens (but not the dorsomedial striatum) disrupts pup retrieval and pup licking, but enhances nursing. In our study, we investigated the effects on maternal behavior of central infusion of haloperidol into the shell part of the nucleus accumbens (NA) (Li, 2002). We used a within-subjects design with each mother rat receiving two doses of haloperidol in a counterbalanced manner. We found that haloperidol at 5.0 μg/μl affected every component of maternal behavior. For example, it significantly impaired pup retrieval and nest building, but it increased pup nursing. This result was

consistent with the systemic haloperidol studies (Stern, 1991; Li *et al.*, 2004), and further demonstrates that the NA shell may be one of the brain sites where haloperidol acts to disrupt maternal behavior.

In summary, recent work on the behavioral, neurochemical and neuroanatomical mechanisms of antipsychotic effects on maternal behavior in rats has suggested that antipsychotic drugs disrupt active maternal responses primarily by suppressing maternal motivation. The sedative effects of atypical drugs also contribute to their disruptive effect. In terms of receptor mechanisms, dopamine D_2 receptors and serotonin 5-$HT_{2A/2C}$ receptors are both involved. D_2 receptors contribute more to the haloperidol (maybe also other typical antipsychotics)-induced disruption of active maternal behavior and its enhancement of pup nursing, while 5-$HT_{2A/2C}$ receptors contribute more to the clozapine-induced disruption. Finally, using the *c-Fos* immunohistochemistry technique and microinjection, we demonstrated that the nucleus accumbens shell is an essential component of the neural system that supports the disruptive effect of antipsychotic drugs. Because much research in this area has been conducted in my laboratory, independent replication would greatly improve the validity of our conclusions.

Clinical implications and future research

As mentioned in the Introduction, studying antipsychotic drug effects on maternal behavior has important clinical implications for understanding the deficient maternal care provided by patients with schizophrenia. Clinical observations suggest that women with schizophrenia have sexual practices similar to those of demographically matched control subjects. Several studies have found that over half of the women with schizophrenia are also mothers, a rate that is comparable with the general population (Seeman, 2004). Like mothers with other mental illnesses, most mothers with schizophrenia raise their own children (Abel *et al.*, 2005), feel the pride of looking after a child, and many demonstrate a desire to take responsibility despite their mental illness and often adverse circumstances (Mowbray *et al.*, 1995). Studies on the mother-child relationship reveal that the quality of maternal care from schizophrenic mothers is generally inferior to that from healthy mothers (Bosanac *et al.*, 2003; Wan *et al.*, 2008b). It has been reported that mothers with schizophrenia show fewer positive emotional responses and less social contact with their infants than do healthy mothers (Persson-Blennow *et al.*, 1984; McNeil *et al.*, 1985; Naslund *et al.*, 1985; Persson-Blennow *et al.*, 1986). They are generally more remote, silent, insensitive, and unresponsive during mother-infant play, and they are less demanding of their infants (Riordan *et al.*, 1999; Snellen *et al.*, 1999). Their interaction with infants is less mutually satisfying, less excited, and more serious (Riordan *et al.*, 1999). Mothers with schizophrenia as a group show more non-responses and more abnormal behaviors as a result of being psychologically withdrawn from the interaction (Wan *et al.*, 2008b). These suboptimal patterns of maternal responding in mothers with schizophrenia are found to be dissociable from infant inertness, negativity or low initiation (Wan *et al.*, 2008b), although some reports show that infants of mothers with schizophrenia are more avoidant than normal infants (Riordan *et al.*, 1999).

A number of contributing factors to this impaired relationship have been identified, including positive and negative symptoms, cognitive deficits, social cognitive impairments,

social stress such as stigma, and a lack of protective factors (Wan *et al.*, 2007). For example, the mother may be inattentive to the needs of her baby because her delusions or hallucinations demand preferential attention. She may also be unavailable to her baby due to a lack of motivation to care for her baby (Snellen *et al.*, 1999). Her attention deficits may severely hamper her interaction skills, such as timely responding to the infant's signals. Her cognitive deficits may affect her ability to provide the appropriate support for her child's cognitive development (Wan *et al.*, 2008a). Therefore, antipsychotic drugs could conceivably improve maternal care in schizophrenic mothers by controlling various symptoms of schizophrenia (especially the positive symptoms) (Seeman, 2004), given their known clinical efficacy against positive and negative symptoms of schizophrenia and cognitive impairments (Meltzer, 2013).

On the other hand, antipsychotic medications could also interfere with parenting – mother patients are aware of the problems of taking antipsychotic drugs but fear the alternatives. Some mothers reported purposely missing their medications in order to stay alert and focused on their child (Seeman, 2004). Mechanistically, it is well known that antipsychotics can give rise to the "neuroleptic-induced deficit syndrome" (NIDS) (Awad, 1993; Awad and Hogan, 1994), a state in which there is poverty of speech, flattened affect, loss of drive, and social withdrawal. Since NIDS's clinical presentations are similar to the negative symptoms of schizophrenia, antipsychotics could conceivably disrupt maternal behavior through similar mechanisms. The preclinical work summarized in this review provides a strong support for this notion, although we need to be careful in assuming that similar behavioral effects would be observed in both normal and "diseased" animals. For human research, as both antipsychotic drugs and schizophrenic symptoms jointly affect maternal care, the key issue is to identify the possible interactive effects of schizophrenic symptoms and antipsychotic medications on the quality of maternal care.

Overall, research in this area not only enhances our understanding of how antipsychotic medications impact the quality of maternal care, but also helps in identifying the relevant psychological and neurobiological mechanisms responsible for antipsychotic action, as well as understanding the neurobiology of maternal behavior. This work will certainly help us develop better psychological and pharmacological intervention strategies to improve maternal care in patients with schizophrenia. For example, if results from this project support our hypothesis that antipsychotics reduce the quality of maternal care by decreasing motivation to care for the young, behavioral interventions based on increasing mothers' motivation to care for the young may have a better chance of being successful. Furthermore, if blocking dopamine D_2 and 5-$HT_{2A/2C}$ receptors turns out to be the main cause of impaired maternal care, pharmacological interventions based on enhancing dopamine D_2- and 5-$HT_{2A/2C}$-mediated transmission may be a valid approach.

One future research will further delineate the neuroreceptor mechanisms of antipsychotic effects on maternal behavior. Because none of the tested antipsychotics targets only one receptor system, and quinpirole and DOI have actions on at least two different receptors (D_2 and D_3 for quinpirole and 5-HT_{2A} and 5-HT_{2C} for DOI), the exact receptor that mediates the maternal-disruptive effect of haloperidol, clozapine and olanzapine is uncertain. It will be important to use more selective agonists or antagonists to help delineate the receptor

mechanisms of antipsychotic action. For example, we may be able to use the selective 5-HT_{2A} receptor antagonist M100907 and the selective 5-HT_{2C} receptor antagonist SB242084 together with DOI to specify the relative importance of 5-HT_{2A} and 5-HT_{2C} receptors in the mediation of the maternal disruptive effect of atypical antipsychotics. Another future project will use highly selective receptor antagonists for D_2, D_3, 5-HT_{2A}, or 5-HT_{2C} receptor to simulate the effects of antipsychotic drugs. For example, we could treat postpartum female rats with either a selective D_2 antagonist raclopride, the 5-HT_{2A} antagonist M100907, or both raclopride and M100907 to see which condition produces a close simulation of the effect of an atypical antipsychotic such as clozapine and olanzapine. Furthermore, we could use double staining techniques to identify the specific types of neurons (dopaminergic, serotoninergic or GABAergic) that show an increase in *c-Fos* expression in response to the antipsychotic treatment.

To further examine the neuroanatomical basis of antipsychotic effects, it will be important to use the information garnered from the *c-Fos* study and examine whether atypicals such as risperidone, quetiapine and aripiprazole also act through the nucleus accumbens shell-related reward neural circuitry to disrupt maternal behavior. Similarly, one could microinject antipsychotic drugs or various dopamine or serotonin agonists or antagonists in various brain regions to examine their possible interactions with antipsychotics. Future work employing this microinjection technique will be necessary to verify the neural systems for each drug. All these behavioral, neuroreceptor and neuroanatomical levels of research should also be conducted in animal models of postpartum psychosis (and depression and anxiety) to enhance their clinical relevance. The use of normal rats is good for isolating the impact of antipsychotic treatment from that of schizophrenia symptoms, but this approach could not delineate the intricate interactions between these two sources of impact on maternal care. In this regard, development and validation of animal models of postpartum psychosis is urgently needed.

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