

The effect of haloperidol on maternal behavior in WAG/Rij rats and its consequences in the offspring

Yulia V. Dobryakova^{1,*}, Vyacheslav A. Dubynin², and Gilles van Luijtelaar³

¹Laboratory of Neurophysiology of Learning, Institute for Higher Nervous Activity and Neurophysiology, Russian Academy of Science, Moscow, Russian Federation, *Email: julkadobr@gmail.com; ²Biological Faculty, Department of Human and Animal Physiology, Moscow State University, Moscow, Russian Federation; ³Donders Centre for Cognition, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen, Nijmegen, the Netherlands

Haloperidol treatment during pre- and post-natal period affects maternal behavior and this may have long-term effects on the offspring. We examined whether early haloperidol administration to Wistar-Albino-Glaxo dams from Rijswijk (WAG/Rij) and in Wistar control rats would affect maternal care and as a consequence, seizure susceptibility and behavior in the WAG/Rij's offspring at 3–4 months of age. Nursing dams of this well-validated genetic animal model of absence epilepsy and control dams were injected with haloperidol or saline at PPD 1 to 6. Maternal behavior was evaluated at PPD 7 to 9. Haloperidol-injected WAG/Rij dams showed more pup carryings compared with saline-injected mothers, this effect was not noticed in control Wistar dams. The offspring of haloperidol-treated WAG/Rij dams, tested during adulthood, showed heightened behavioral activity (time spent into the open arms, head dips) in the elevated plus-maze, as well as shorter spike-wave discharges (SWD) as measured in their electroencephalographic activity compared with saline-treated rats. Overall, it can be concluded that deviancies in the DA system as induced by haloperidol facilitates pup carrying/retrieval behavior in WAG/Rij rats and reduces seizure activity of the offspring in adulthood. Therefore, inter-individual differences in seizure properties and behavior in genetically predisposed animals may be due to differences in maternal behavior of the dams.

Key words: absence epilepsy, dopaminergic system (DA system), genetic animal model, haloperidol, maternal behavior, spike-wave discharges (SWD), WAG/Rij rats

INTRODUCTION

The dopaminergic (DA) system is one of the neuro-modulator brain systems involved in the initiation and maintenance of maternal behavior (Byrnes et al. 2002). This is well documented and supported by outcomes from microdialyses, immunocytochemical, pharmacological and behavioral studies (Hansen et al. 1991, 1993, Hansen 1994, Stern and Keer 1999, Dobryakova et al. 2006). Maternal behavior of rats is accompanied by activation of D1 receptors in the nucleus accumbens (n. Acc) and presentation of pups to lactating dams increases extracellular DA (Hansen et al. 1993) and cFos expression in the n. Acc (Fleming et al. 1994). Electrolytic lesion of the n. Acc before or immediately

after parturition affects retention of maternal behavior 10 days later and DA-depleting 6-OHDA lesions of n. Acc or DA cell bodies in the ventral tegmental area (VTA) disrupt maternal behavior (Hansen 1994, Lee et al. 1999). Furthermore, also systemic and central injections of DA antagonists (haloperidol, clebopride) disrupt maternal (Spear et al. 1980, Byrnes et al. 2002, Dobryakova et al. 2006). Finally, individual differences in maternal licking/grooming behavior are directly related to variations in magnitude of the DA signal in the n. Acc (Champagne et al. 2004).

Differences in maternal care contribute to inter-individual developmental differences of pups and may have long-term effects in adulthood (Cameron et al. 2005). To illustrate, intense maternal licking accelerates the time of eye opening and reduces fear in the offspring (Uriarte et al. 2007). Earlier studies have shown that the treatment of lactating dams with neuroleptic drugs disrupts maternal behavior and induced

Correspondence should be addressed to Y.V. Dobryakova
Email: julkadobr@gmail.com

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hyperactivity in their offspring at 4 weeks of age and abnormally low level of activity another 4 weeks later (Ahlenius et al. 1977).

The current study uses the Wistar-Albino-Glaxo/Rijswijk (WAG/Rij) rat strain. The phenotype of these rats, fully inbred (subjects are genetically homozygous for all autosomal chromosomal alleles), is characterized by spontaneously occurring spike-wave discharges (SWDs) and concomitant clinical characteristics such as behavioral immobility, mild facial myoclonus, movements of the vibrissae and reduced responsiveness to environmental stimuli and mild symptoms of depression (van Luijtelaar and Sitnikova 2006, Sarkisova and van Luijtelaar 2011). The strain is well validated as a genetic absence epilepsy model with comorbidity for depressive-like symptoms (Depaulis and van Luijtelaar 2006, Sarkisova and van Luijtelaar 2011). WAG/Rij rats are quickly developing catalepsy and exhibit different neurochemical (DA) profiles compared to Wistars (Kuznetsova et al. 1996, de Bruin et al. 2001, Birioukova et al. 2005). It was previously established that maternal behavior of WAG/Rij dams is poorer compared to Wistar controls. WAG/Rij rats had consistently less approaches to the pups, pups carrying/retrieval and higher pup approach latencies compared to Wistar dams (Dobryakova et al. 2008). We have proposed that the reduction in maternal care is probably due to complex changes in the WAG/Rij's DA system.

The first aim of the study was to examine the effect of repeated haloperidol injections during the early postpartum period on maternal behavior of WAG/Rij and Wistar control rats. Since maternal care is pup-directed in the early postpartum period (Rosenblatt 1969, Mattson et al. 2001, Pereira and Morrell 2009), a previous developed paradigm in which pup retrievals and latencies are the most important variables was used (Dobryakova et al. 2006). The second aim was to investigate whether differences in maternal care in WAG/Rij rats would affect behavior (elevated plus maze, open field) and seizure susceptibility (as measured with electrocorticogram ECoG) during adulthood in their offspring.

METHODS

Animals

Thirteen experimentally naïve female WAG/Rij rats, born and raised at the vivarium of Biological Psychology, Donders Centre for Cognition, and 16 female Wistar rats, born and raised at the vivarium of

Research Center of Biomedical Technology RAMS (nursery "Stolbovaya"), all approximately 90-days old, were used. After pairing with conspecific males, pregnant females were individually housed in standard macrolon cages (27 × 19 × 11 cm) with food and water ad libitum in a room with a 12-hours light/dark cycle (light off at 07:00 AM). Parturition day was noted as post-partum day 0 (PPD 0); these mothers were used in maternal behavior testing (Experiment I); next, random chosen male offspring ($n=20$) from the WAG/Rij dams were used (Experiment II). All litters of the same rat strain were born within a week period and were weaned at PPD 30. The average litter size of the WAG/Rij's was 7.5 ± 0.6 pups (range: 4–11; mean \pm SEM), of the Wistar rats 10 ± 0.9 pups (range: 8–14; mean \pm SEM). Subsequently, they were housed in groups of 2 animals of the same sex under the same laboratory conditions. The protocol of the experiments was approved by the Medical-Ethical Committee of Radboud University Nijmegen (RU-DEC) and the Bioethical Committee of Moscow State University. All efforts were done to minimize the number of animals used, and their suffering.

Experiment I

Behavior registration – maternal behavior test

Two groups of WAG/Rij and Wistar dams were created at PPD 1. WAG/Rij and Wistar dams of the first group (I-WAG/Rij, $n=7$; I-Wistar, $n=8$) received haloperidol (0.1 mg/kg, i.p.) from PPD 1 to 6, this dose was chosen because it has been shown to disrupt active maternal behavior without an effect on locomotor activity (Lonstein and Fleming 2002, Dobryakova et al. 2008). WAG/Rij ($n=6$) and Wistar dams ($n=8$) of the second group (II) received the same volume saline i.p. also from PPD1–6. The daily injections occurred approximately at the same time of day. The experiments in WAG/Rij rats in Nijmegen and in Wistar rats in Moscow were both performed by YVD, it guaranteed that the behavioral procedures were identical in both laboratories.

Maternal behavior was observed on PPD 7–9 in an open field arena always at the same time of day (10:00 AM–01.00 PM). This arena (diameter 80 cm) was encircled with a wall (height 40 cm). Two bulbs provided bright light (180 lux) in the centre and 140–160 lux along the edges. A 15 W red bulb pro-

vided 4.1 lux in the centre and 2.5–3.5 lux along the edges. An empty Petri dish was placed in the centre.

Maternal behavior and general activity observation were based on previous literature (Silva et al. 2001, Lonstein and Fleming 2002) and on our previous studies, where open field parental behavior measures were evaluated and used (Dobryakova et al. 2006, 2008). The presently used test evaluates maternal behavior and maternal motivation during short time periods (approximately 10 min per animal/per day). It has been shown that maternal behavior observation in the nest might not differ between two different groups, in contrast to the currently used “retrieval test” (Braw et al. 2009). Our test might be more sensitive than observation in the home cage. At the test day, dams were taken to the experimental room to allow them to adapt for 30 min. Testing involved three daily observation periods of two minutes, first in the absence of pups under red light, next maternal behavior was observed 2 times 2 minutes under red and bright light conditions in the presence of pups.

After the adaptation period, dams were placed in the arena (near the wall) and their horizontal (number of sectors passed; movements along the sectors of the open field) and vertical activity (rearings; standing on her two hind legs), grooming (cleaning her body using her tongue/paws) were determined by observation during 2 min under red light; this has been called observation period 1.

In the second observation period 3 pups were placed in the Petri dish in the middle of the round open field. Dams were placed in the arena with the pups after 1 min of rest in the home cage. Maternal observation was recorded for 2 min under red light. In this part of the experiment the following parameters were recorded: (1) latency of the first approach to the dish with pups; (2) number of approaches to the dish; (3) number of pup carrying/retrieval (the pups were picked up/moved to another location); (4) latencies of each pup carrying/retrieval.

In the third observation period 3 pups were again placed in the Petri dish in the middle of the open field. Dams were placed in the arena with the pups after 1 min of rest in the home cage. Maternal behavior was now observed under bright light. The same parameters of maternal behavior were recorded for 2 minutes.

Experiment II

Behavior of the offspring

This concerns only WAG/Rij rats. Ten random chosen male offspring from haloperidol-treated and 10 from control dams were used for behavioral and ECoG studies. They were approximately 4 month old and were housed in groups of two. Exploratory and emotional behavior was assessed in the round open and square open field and elevated plus-maze, one test per day on 3 subsequent days, all rats were exposed to the same test order. After that the rats underwent surgery and ECoG recording.

Exploratory and emotional behavior was studied in the same round open field (but without Petri dish). Each rat was placed in the middle of the arena and its horizontal (number of sectors) and vertical activity (rearings), grooming and entries to the centre of the arena were quantified during 5 min: first under bright light (3 min), next 1 min under red light, and one more minute under bright light.

The square (1×1 m) open field was enclosed with 30 cm height walls. Each rat was placed in the same corner of the arena and the rat's behavior was recorded automatically for 10 min under red light using Ethovision software (Noldus, Wageningen, NL). Red bulbs provided 4.1 lux in the centre and 2.5–3.5 lux along the edges. The following behavioral variables were quantified: total distance moved (cm), velocity (cm/s), movement frequency and total movement duration (s).

The elevated plus-maze had two open (35×10 cm) and two closed arms with lateral and terminal boards ($35 \times 10 \times 20$ cm) extended from the central platform (5×5 cm). The maze was elevated to a height of 50 cm from the floor. Two electric bulbs provided 180 lux in the open and 40–50 lux in the closed arms. A session began with the insertion of an animal into the central platform. The test lasted 3 min. The following parameters were scored (Roman et al. 2006): latency of the first enter into a closed arm from the central platform with all four paws, time spent into the open and closed arms, the number of head dips (rat nose below level of floor of the arm), stretch attend postures from closed arms (the animal stretched its body from the dark compartment toward the centre), the total arms entries, number of rearing and grooming periods.

Implantation of ECoG electrodes and ECoG recordings in the offspring

Tripolar epidural electrodes (MS 333/2A, Plastic One Inc., Roanoke, VA, USA) were implanted under Isoflurane inhalation anesthesia (2.5%) after the end of the behavioral study. Coordinates were according to the atlas of Paxinos and Watson (1998) with bregma as reference. One active electrode was situated in the frontal (bregma zero-zero: A 2.0, L -3.5), the second in the parietal region (A -6.0, L -4.0). The ground electrode was placed over the cerebellum. Rats were given 10 days for recovery from brain surgery.

The offspring was housed in individual recording cages for habituation to the experimental conditions for 16 hours prior to the start of the ECoG recording session. Differential ECoG's (1–100 Hz was allowed to pass, sample rate 256/s) were continuously made in free moving animals for 4 hours (between 09:00 AM and 01:00 PM), always at the same time of day. The data acquisition system was WINDAQ Software (Dataq Instruments, Akron, OH, USA). The number, total and mean duration of SWDs were quantified according to well-known criteria (van Luijckelaar and Coenen 1986).

Statistical analysis

Behavioural data are presented as mean \pm SEM. Maternal behavior data were analyzed using a factorial repeated measures analysis of variance (ANOVA) and Student's independent *t*-test to estimate possible dif-

ferences between groups (between subjects) and days (within subjects). Behavioral activities of the offspring in the round and square open fields and elevated plus-maze were evaluated with a 2-way ANOVA with minutes and group as within and between subjects factors respectively, when a significant interaction or day effect was found, *post-hoc* test (LSD) were used to reveal group differences on separate days or differences between days. The differences in seizure parameters were tested with Student *t*-test. *P*-values <0.05 were considered as statistically significant.

RESULTS

Maternal behavior (Experiment I)

There were no significant differences between the haloperidol and saline treated WAG/Rij dams for the non-maternal activities such as distance moved, rearing, and grooming as measured during observation period 1. There was however a significant group effect with haloperidol-treated WAG/Rij dams exhibiting more pup carrying/retrieval compared to controls ($F_{1,11}=5.99$, $P<0.05$) in observation period 2, the outcomes are presented in Figure 1A. Although haloperidol had no effect on the number of approaches throughout PPD 7 to 9, haloperidol-treated dams showed a higher number of pup approaches on PPD 9 compared to PPD 7 ($P<0.05$; see Fig. 1B), while saline injected WAG/Rij dams didn't. The same significant group effect was found for the number of pup's carry-

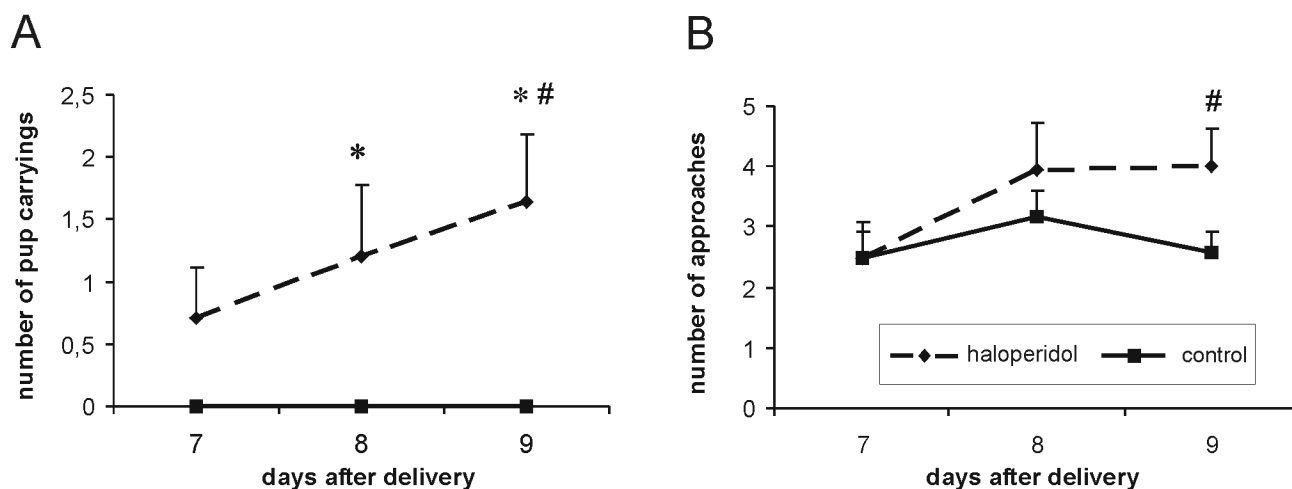


Fig. 1. Number (mean \pm SEM) of pup carryings (A) and the number of approaches (B) in the maternal behavior test shown by WAG/Rij dams from the two groups tested: chronic (PPD1–6) haloperidol-treated and control (saline) rats ($n=6-7$ /group). * $P<0.05$, different from saline. # $P<0.05$ different from PND 7.

ing/retrieval ($F_{1,11}=5.48$, $P<0.05$) in observation period 3 (bright light). There was no any effect of haloperidol on the latencies of the approaches to the pups. However, there was a group effect for the latency to the first pup carrying in observation period 2: the haloperidol treated dams had lower latencies ($F_{1,11}=6.81$, $P<0.05$) than control rats. The same group ($F_{1,11}=5.1$, $P<0.05$), day ($F_{2,22}=3.54$, $P<0.05$) and interaction between group and day ($F_{2,22}=3.54$, $P<0.05$) effects were found for the latency of the first pup carrying in observation period 3 (bright light). Latencies of haloperidol treated dams were shorter and decreased from PPD 7 to 9.

There were no significant group (haloperidol) and control Wistar dams on PPD 7 to 9 on any of the maternal and non-maternal behaviors.

Behavior of the offspring (Experiment II)

The analyses of the offspring's behavior which was observed at first, in the round open field test for a period of 5 min didn't show significant group effects. A significant time effect ($F_{4,72}=27.5$, $P<0.0001$; $F_{4,72}=6.9$, $P<0.0001$) was noticed for the number of sectors passed and rearings, respectively. In both cases the *post-hoc* test revealed that the activity significantly decreased over the first 3 minutes ($P<0.001$) and that the number of sectors crossed and rearings in the red light at the 4th minute were significantly higher than in the bright light at the 3rd and 5th minutes (P 's<0.0001).

The square open field test (10 min, red light) did not show significant group effects, however there was a significant time effect for distance moved ($F_{9,162}=20.82$, $P<0.0001$), velocity ($F_{9,162}=20.79$, $P<0.0001$) and movement duration ($F_{9,162}=2.59$, $P<0.01$). All these parameters decreased over time.

The analyses of the elevated plus-maze data (3 min) showed that the offspring from haloperidol-treated dams (group I) exhibited significantly longer time in the open arms ($F_{1,18}=9.3$, $P<0.01$) of the maze than the control group, the results are depicted in Figure 2A. Also the number of head dips and the total number of arm entries were significantly higher in animals from group I ($F_{1,18}=6.8$, $P<0.05$; $F_{1,18}=4.6$, $P<0.05$, respectively) compared to from group II.

ECoG recording

All WAG/Rij offspring showed SWDs, independent of the postnatal manipulations of their mothers (haloperidol-treated or control dams). The mean duration and the total duration of SWDs were shorter in the haloperidol-treated group (mean $F_{1,17}=4.2$, $P<0.056$ and total duration $F_{1,17}=7.3$, $P<0.015$ of SWDs, respectively). Also the number of SWD in the offspring from haloperidol-treated rats tended to be shorter compared to control ($F_{1,17}=3.5$, $P<0.08$; data presented in Fig. 2B).

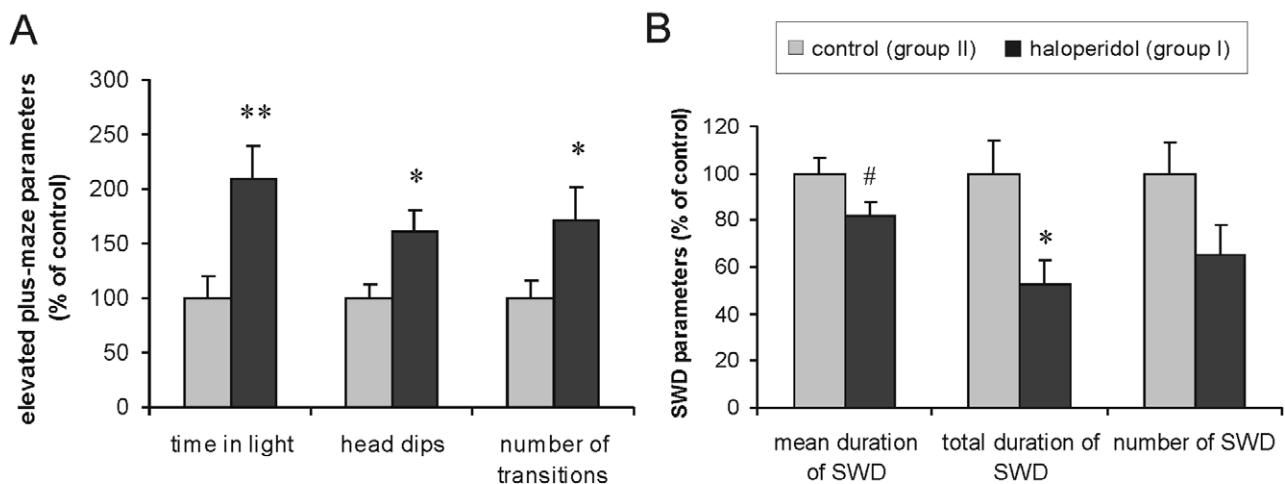


Fig. 2. Mean amount of time (s) in light, number of head dips and total arms entries (mean and SEM) (A) shown by the offspring groups in the elevated plus-maze test ($n=10$ /group). Mean duration (mean \pm SEM), total duration and number of SWDs (B) shown by the offspring groups in the ECoG recording ($n=10$ /group). * $P<0.05$; ** $P<0.01$, # $P<0.056$, different from control.

DISCUSSION

In this study the effects of haloperidol on maternal behavior and behavior of the offspring during adulthood in genetic epileptic WAG/Rij and in Wistar control rats were examined. The outcomes of this study demonstrated that early daily (PPD 1–6) haloperidol administration to the WAG/Rij mothers, no longer being under the direct influence of haloperidol, showed what can be called an increase in maternal behavior at PPD 7–9 compared to control. More specifically, haloperidol-treated WAG/Rij rats showed more pup carryings/retrievals and reduced latencies to the first pup carrying compared to control injected WAG/Rij dams. The results are at variance with most of the literature on the effects of antipsychotic drugs on maternal behavior (Li et al. 2004, 2005a, Zhao and Li 2009); generally an inhibition of active maternal responses is found after haloperidol treatment. On the one hand, it can be supposed that the increase in maternal behavior might be due to a withdrawal effect: plasma level of haloperidol (0.25 mg/kg) decreased from 2 to 24 hour after the last injection (Li et al. 2005a). Nevertheless, the effects of repeated administrations may persist several days after cessation of drug administration. It has been shown that at low doses haloperidol dose-dependently reduces intromission frequency, and that this effect of repeated administration persists 4 to 5 days after cessation of haloperidol administration (Tupala et al. 1999). Moreover, our results in Wistar rats showed that daily haloperidol administration from PPD 1 to 6 did not change locomotion, exploratory and maternal behavior on PPD 7 to 9. Therefore, it seems that the increase in maternal behavior induced by haloperidol is indeed unique for WAG/Rij rats. WAG/Rij rats are known to have a low activity of the nigrostriatal and high reactivity of the mesolimbic DA system (de Bruin et al. 2001). Analysis of the different brain structures showed also modified density of DA receptors: WAG/Rij rats have lower number of D1-like DA receptors in the nucleus accumbens and increase density of D2-like receptors in frontal and parietal cortical regions compared to non-epileptic ACI rats (Birioukova et al. 2005). Moreover, WAG/Rij rats are quite sensitive for by haloperidol induced catalepsy (Kuznetsova et al. 1996). These data illustrate the differences in WAG/Rij rat nature and the differences in their DA system.

Maternal behavior has two components: motor and motivational. Typical antipsychotic drugs such as halo-

peridol are known to induce motor deficits. Our data indicate that postpartum treatment of the mothers with haloperidol or saline does not cause differences in locomotor activity in the dams of both strains. Instead, the increase in pup carryings/retrievals in WAG/Rij may closely associate with their motivational effect. It is of interest that the depressive-like phenotype of WAG/Rij rats has also been explained by changes in the DA system (Sarkisova and van Luijtelaar 2011).

Increased amount of maternal activity (heightened number of pup carryings, shorter latencies and increased number of approaches over testing days) after drug treatment in WAG/Rij mothers might be due to the low concentration of haloperidol that was used in combination with the above mentioned differences in their DA system. It is well-known that acute antipsychotic drug injections with the same dose as we used, disrupt the active components of maternal behavior such as pup licking, pup retrieval and nest building as was established in Sprague-Dawley rats (Silva et al. 2001, Li et al. 2004). It is generally assumed that antipsychotic drugs act mainly through a blockade of postsynaptic D2 receptors (Kapur and Mamo 2003). Nevertheless, it has been shown that in low doses some antipsychotic drugs such as amisulpiride enhance pup licking (Li et al. 2005b), most likely by a preferential block of pre-synaptic dopamine auto-receptors that control the synthesis and release of DA (Missale et al. 1998). It can be speculated that in WAG/Rij rats a low dose of haloperidol acts on auto-receptors and increases the release of DA, and stimulates active maternal behavior. There is some indirect evidence to support this view: low dose of dopamine agonists can act behaviorally and biochemically as DA antagonist (Skirboll et al. 1979). Chronically administered low doses of haloperidol early in life were shown to block auto-receptors in the mesolimbic DA terminal regions and to enhance DA concentrations (Scalzo and Spear 1985). Note also that the effect of chronic administration of haloperidol on complex behavior such as maternal behavior could be different from acute administration. It has been shown that chronic haloperidol administration reduced NMDA receptor sensitivity in contrast to acute injections (Jardemark et al. 2000).

The behavior in the square open field of the offspring of haloperidol treated WAG/Rij mothers was not affected. Only time effects for all three parameters of locomotor activity (total distance moved, velocity and total movement duration), independently of treat-

ment, were found. This reflects an adaptation or habituation of the animals to the test condition: the duration of the test (10 min) allowed that the animals adapt since the time effect was not or much less obvious in the round arena and elevated plus maze (these tests lasted 5 and 3 min, respectively). It was found that offspring from the chronically haloperidol-treated mothers, tested in the elevated plus-maze test, showed significantly more time in the light arms. This is commonly interpreted as a low anxiety level. Moreover, locomotor activity of the offspring from haloperidol treated rat dams that were measured here by total arms entries, were significantly higher compared to control dams. These results led to the suggestion that the offspring from haloperidol-treated dams show more interest in their environment, are active in investigating their environment and have a lower anxiety level compared to the offspring of control mothers.

The behavioral studies show that early treatment of the WAG/Rij dams with haloperidol reduced anxiety of the offspring. Considering that haloperidol changes maternal behavior (Spear et al. 1980, Li et al. 2005a, Pereira and Ferreira 2006), present data proposed that behavioral differences in the offspring are due to different level of maternal care between haloperidol-treated and untreated dams.

The current study's findings also showed that early haloperidol administration reduced the total duration of SWD, with tendencies on both mean duration and number of SWD. Earlier findings showed that various characteristics of SWD (number, mean duration or amplitude) are differently sensitive for environmental factors such as housing conditions (enriched versus isolated housing) or neonatal handling and maternal deprivation (Schridde and van Luijtelaaar 2004, Schridde et al. 2006). Studies in other multifactorial genetic models of idiopathic generalized epilepsy, the El mice, showed that parental investment and early stress is also able to affect seizure and locomotor activity phenotype in the adult offspring (Bond et al. 2003).

Besides differences in maternal care it is also possible that the drug has indirect effects on the pups through the milk since haloperidol can get into milk and influences the behavior of the offspring, both when they are pups and consequently, later in life (Lundborg and Roos 1974, Gentile 2004). Also body weight, ultrasonic vocalization and the physical state of newborns might influence parental behavior of the mothers as well and affect the phenotype (Hashimoto et al. 2001).

Moreover, haloperidol induced behavioral changes were dependent of the age at which the animals were tested (Ahlenius et al. 1977, Spear et al. 1980). Behavioral effects of prenatal haloperidol exposure follow a dynamic changing with age. Early reductions in behavior can be replaced by an actual increase as haloperidol pups approach adulthood (Scalzo et al. 1989).

CONCLUSION

In summary, early and low dose of haloperidol increases maternal behavior in WAG/Rij rats. This seems unique for WAG/Rij rats. Moreover, haloperidol administration of the mothers reduced anxiety and seizure properties in the offspring at adulthood. These outcomes demonstrates that maternal care has long lasting behavior effects in this genetic model for idiopathic epilepsy and that intra-interindividual differences in EEG and behavior can be due to differences in maternal care.

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