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Social behaviour in rats lesioned with ibotenic acid in the hippocampus: quantitative and qualitative analysis

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Abstract *Rationale:* Neonatal ibotenic acid lesion of the ventral hippocampus was proposed as a relevant animal model of schizophrenia reflecting positive as well as negative symptoms of this disease. Before and after reaching maturity, specific alterations in the animals' social behaviour were found. *Objective:* In this study, social behaviour of ventral hippocampal lesioned rats was analysed. For comparison, rats lesioned either in the ventral hippocampus or the dorsal hippocampus at the age of 8 weeks were tested. *Methods:* Rats on day 7 of age were lesioned with ibotenic acid in the ventral hippocampus and social behaviour was tested at the age of 13 weeks. For comparison, adult 8-week-old rats were lesioned either in the ventral or the dorsal hippocampus. Their social behaviour was tested at the age of 18 weeks. *Results:* It was found that neonatal lesion resulted in significantly decreased time spent in social interaction and an enhanced level of aggressive behaviour. This shift is not due to anxiety because we could not find differences between control rats and lesioned rats in the elevated plus-maze. Lesion in the ventral and dorsal hippocampus, respectively, in 8-week-old rats did not affect social behaviour. *Conclusions:* The results of our study indicate that ibotenic acid-induced hippocampal damage per se is not related to the shift in social behaviour. We favour the hypothesis that these changes are due to lesion-induced impairments in neurodevelopmental processes at an early stage of ontogenesis.

Key words Schizophrenia · Hippocampus · Ibotenic acid · Social behaviour · Anxiety · Animal model

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Introduction

Schizophrenia is presently viewed as a complex and heterogeneous disease based on neurodevelopmental derangements involving several neurotransmitters and neuromodulators (Weinberger 1987; Bogerts 1997; Persico and Macciardi 1997; Cannon and Murray 1998). Typical symptoms are auditory hallucinations, delusions or disorganised thought processes (referred to as positive symptoms) and flat affect, decreased drive or diminished social interaction (negative symptoms) (Howard 1997). Despite intensive research, the pathophysiology of schizophrenia remains largely unknown.

Ibotenic acid lesion of the ventral hippocampus in neonatal rats (Lipska et al. 1993) was shown as an animal model with constructive and predictive validity to address neurodevelopmental aspects of schizophrenia (Lipska and Weinberger 1997). In a number of different experimental paradigms, typical alterations in the behaviour of lesioned animals or in neurotransmission were found before and after puberty:

- Significantly reduced prepulse inhibition (Lipska et al. 1995b).
- Disruption in latent inhibition (Grecksch et al. 1999).
- Behavioural hyperresponsiveness to amphetamine (Lipska et al. 1993; Wan et al. 1996; Wan and Corbett 1997).
- Modulation of haloperidol-induced catalepsy and apomorphine-induced stereotyped behaviour (Lipska et al. 1995a).
- Alterations in dopaminergic and glutamatergic neurotransmission (Lipska et al. 1992; Lipska and Weinberger 1996).
- Significantly increased levels of D_2 receptors in rats 60 days after ibotenic acid lesion (Flores et al. 1996).

Sams-Dodd et al. (1997) examined the effect of the neonatal hippocampal lesion on social behaviour. After puberty, lesioned rats demonstrated a significant reduction in active social interaction. The authors concluded that neonatal hippocampal lesion in the rat models

some positive as well as negative aspects of schizophrenia.

According to Kay et al. (1987), negative symptoms represent behavioural patterns that are reduced compared with the normal state and include social withdrawal, blunted affect and poor report. In this respect, it would be of interest to perform a detailed analysis of social behaviour in ibotenic acid hippocampal lesioned rats concerning non-aggressive and aggressive components. For that purpose, rats were lesioned at day 7 after birth and their social behaviour was tested at the age of 13 weeks. For comparison, adult 8-week-old rats were lesioned in either the ventral or the dorsal hippocampus and tested in the same paradigm at the age of 18 weeks.

Material and methods

For all procedures followed, ethical approval was sought prior to the experiments according to the requirements of the National Act on the Use of Experimental Animals (Germany).

Animals

Pairs of breeders (permanent breeding) of Sprague-Dawley rats (Shoe:SPRD, Tierzucht Schönwalde GmbH) were housed in Macrolon type IV cages in an animal room under controlled climate conditions (temperature 20±2°C, relative air humidity of 55–60%, light/dark cycle of 12:12, light on at 6:00 a.m.). The rats had free access to commercial pellets (Altromin 1316) and tap water. After birth, the number of pups per litter was balanced to eight to ten. Male pups were weaned 21 days after birth and housed in groups of four or five animals in Macrolon type IV cages in the same room where the parents were sheltered. After week 4 of life, rats were fed with Altromin 1326 pellets.

Surgical procedure

Neonatal rats

Rat pups were lesioned in the ventral hippocampus on day 7 of age. The animals were anaesthetised by hypothermia. After placing in a modified stereotaxic apparatus, an incision was made in the skin overlying the skull and 0.3 µl ibotenic acid (Sigma, 15 µg/µl) or sterile physiological saline was infused bilaterally into the ventral hippocampus (AP=–2.8 mm, ML=3.5 mm, VD= 5.0 mm, relative to bregma) at a rate of 0.15 µl/min. The injector was withdrawn 3 min after completion of the infusion and the incision was closed with surgical tissue adhesive (Histoacryl, B. Braun Surgical GmbH, Melsungen, Germany). The pups were placed on an electric warming pad and then returned to their parents.

Adult rats

For the lesion in adult rats, 8-week-old male Sprague-Dawley rats bred as described above were deeply anaesthetised with IP 40 mg/kg Nembutal. The animals were placed in a stereotaxic frame. An incision was made, the skull was trepanated (diameter 0.5 mm) and 0.5 µl ibotenic acid (15 µg/µl) were infused either into the ventral hippocampus (bregma 1 mm above lambda, ML=4.5 mm, AP=–3.0 mm, VD=7.3 mm, relative to bregma; Paxinos and Watson 1986) or the dorsal hippocampus (bregma 2 mm above lambda, ML=3.1 mm, AP=–3.1 mm, VD=3.1 mm, relative to bregma; Paxinos and Watson 1986) as described above.

Ibotenic acid-induced lesion in the dorsal hippocampus in adult rats is unrelated to this model of schizophrenia. These animals were used as an additional experimental group to differentiate between effects due to hippocampal damage and effects related to lesion-induced impairments in neurodevelopmental processes.

Behavioural testing

Animals lesioned at day 7 of life were tested 12 weeks after surgery in the social interaction test when the animals were 13 weeks old. Another group of rats lesioned in the ventral hippocampus at the age of 7 days was tested in the elevated plus-maze when the animals were 13 weeks old. Adult animals lesioned either in the ventral or the dorsal hippocampus at the age of 8 weeks were tested at the age of 18 weeks. Testing was carried out between 8:00 and 12:00 a.m. In the present study, only male rats were used.

Social interaction test

The general design of the model was adapted from File (1993). The test was performed in an open arena (100 cm×100 cm× 40 cm). The floor was made of smooth black polyvinyl chloride. A video camera on the ceiling of the experimental room was used to score the animals' behaviour in an adjacent room. Lighting in the room was 30 lux and was diffused to prevent shadow in the test arena.

Ten days prior to testing, rats were singly housed (Macrolon type II cages with food and water ad libitum). The cages were located together in racks so that auditory and olfactory contact was maintained.

Two days prior to the test, the animals were familiarised with the arena. For that purpose, each animal was given two 7-min trials (one per day) to explore the apparatus. Between each test, the apparatus was cleaned and wiped. The day prior to testing, rats were allocated to test partners on the basis of pre-treatment (i.e. lesioned with ibotenic acid or infusion of sterile saline solution) and body weight. The difference between the two partners of the same status (i.e. lesioned with lesioned or sham with sham) was within 20 g.

Social behaviour was tested for a 7-min period. The time spent in social interaction was scored and separated into non-aggressive (sniffing, following and grooming the partner, social play) and aggressive behaviour (kicking, boxing, wrestling, aggressive grooming, biting). Each pair was used once only.

After each trial, the test arena was cleaned and wiped.

Elevated plus-maze

The plus-maze was made of black polyvinyl chloride and had two open and two closed arms (50×10×40 cm) mounted 50 cm above the floor. The floor of the arms was smooth. White fluorescent tubes were mounted above the maze so that all arms were equally illuminated with 300 lux. For this experiment, separate groups of animals (singly housed) were used.

The rat was placed in the central platform of the apparatus facing an enclosed arm. A camera on the ceiling of the test room was used to score the animal's behaviour from an adjacent room for a 7-min test period by a person blind to the animal's treatment. We measured the number of entries into open and closed arms and the time spent there. Arm entry was defined as all four feet in the arm.

The maze was cleaned following each trial.

Histological investigation

After completion of the experiments, the rats were deeply anaesthetised with an overdose of chloral hydrate. After decapitation, the brains were quickly removed from the cranium, fixed in 8% formalin and embedded in paraffin. The specimens were cut into 6

µm thick coronal sections using a microtome. Every tenth section was Nissl-stained and subjected to morphological inspection under a light microscope (Leitz).

In order to prove whether possible behavioural differences between neonatally lesioned and adult-lesioned rats are attributable to the time of damage or/and the size of the lesion, we studied by planimetry the dimensions of the tissue lesions from the most rostral to the most caudal aspects (five to seven sections per animal). Right ventral hippocampi of five rats from each group were compared. Sections were coded before the estimation and presented to the investigator in a random manner (i.e. the investigator was blinded to the diagnosis). The atlas of Paxinos and Watson (1986) served as a reference. In animals with ibotenic acid administration into the dorsal hippocampus the treatment was regarded successful if the lesion was restricted to both dorsal hippocampi without having affected the ventral part of the hippocampus or other brain areas.

Statistics

The statistical analysis was based on Mann-Whitney *U*-test (SPSS+ software). A *P*-value ≥0.5 was considered significant. All data are presented as medians±deviation of the median.

Results

Ibotenic acid lesion in the ventral hippocampus in 7-day-old rats resulted in significant impairments in social behaviour when tested at the age of 13 weeks. As shown in Fig. 1, lesioned rats spent significantly less time in social interaction [$U(2,12,9)= 18$, $P=0.01$]. The ratio of non-aggressive to aggressive behaviour (calculated on the basis of time spent in social interaction) was 79.9:20.1% in saline-injected control rats and 39.9:60.1% in lesioned rats [non-aggressive control versus lesioned and aggressive control versus lesioned $U(2,12,9)=11$, $P<0.01$ for each]. Interestingly, ibotenic acid lesion in 8-week-old rats either in the ventral or the dorsal hippocampus did not alter social behaviour when the animals were tested at the age of 18 weeks (Fig. 2, Fig. 3). There were no differences in total time spent in social interaction [ventral hippocampus control versus lesioned $U(2,13,16)=82$, $P=0.33$, dorsal hippocampus control versus lesioned U(2,9,8)=25.5, $P=0.31$] or the ratio of non-aggressive to aggressive behaviour [ventral hippocampus control 99:1%, lesioned 95.3:4.7%, non-aggressive control versus lesioned, $U(2,13,16)=90.5$, $P=0.54$, aggressive control versus lesioned U=82.5, $P=0.33$; dorsal hippocampus ratio non-aggressive:aggressive in saline-injected rats 97.05:2.95%, lesioned 90.7:9.3%, non-aggressive and aggressive (control versus lesioned) $U(2,9,8)=30.0$, $P=0.56$ for each].

To find out whether anxiety contributes to differences found in rats lesioned in the ventral hippocampus at the age of 7 days, an additional test with singly housed animals was carried out in the elevated plus-maze when the rats were 13 weeks old. Figure 4 clearly indicates that no differences between the experimental groups occurred in the parameters time% spent on closed arms [$U(2,9,7)= 31.5$, $P=1.0$] and total arm entries [$U(2,9,7)=29.5$, $P=0.46$].

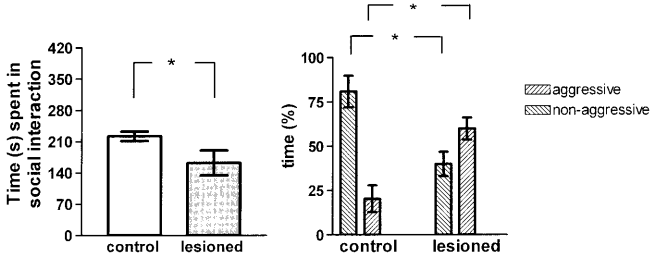

Fig. 1 Social behaviour in rats neonatal lesioned with ibotenic acid in the ventral hippocampus. Age at testing was 13 weeks. *Left panel*: time (s) spent in social interaction, *right panel*: time(%) of non-aggressive and aggressive behaviour in saline-injected control animals and lesioned rats. Control group *n*=9 pairs, lesioned rats *n*=7 pairs. Median±deviation of the median, **P*>0.05

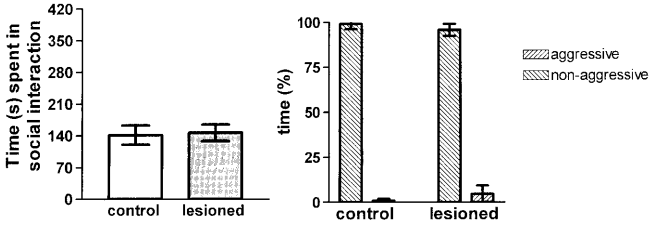

Fig. 2 Social behaviour in rats lesioned with ibotenic acid in the ventral hippocampus at the age of 8 weeks. Age at testing 18 weeks. *Left panel*: time (s) spent in social interaction, *right panel*: time(%) of non-aggressive and aggressive behaviour in saline-injected control animals and lesioned rats. Control group *n*=13 pairs, lesioned group *n*=16 pairs. Median±deviation of the median

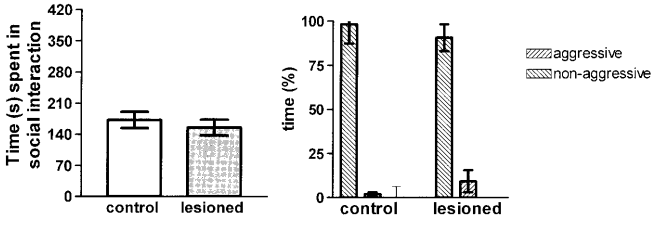

Fig. 3 Social behaviour in rats lesioned with ibotenic acid in the dorsal hippocampus at the age of 8 weeks. Age at testing 18 weeks. *Left panel*: time (s) spent in social interaction, *right panel*: time(%) of non-aggressive and aggressive behaviour in saline-injected control animals and lesioned rats. Control group *n*=9 pairs, lesioned rats *n*=8 pairs. Median±deviation of the median

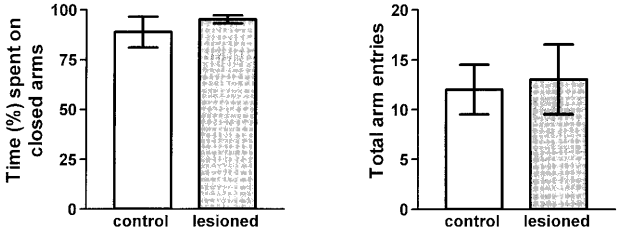

Fig. 4 Behaviour of rats neonatally lesioned with ibotenic acid in the ventral hippocampus in the elevated plus-maze. Age at testing 13 weeks. *Left panel*: percentage of time spent on closed arms, *right panel*: total arm entries. Control group *n*=9, lesioned rats *n*=7

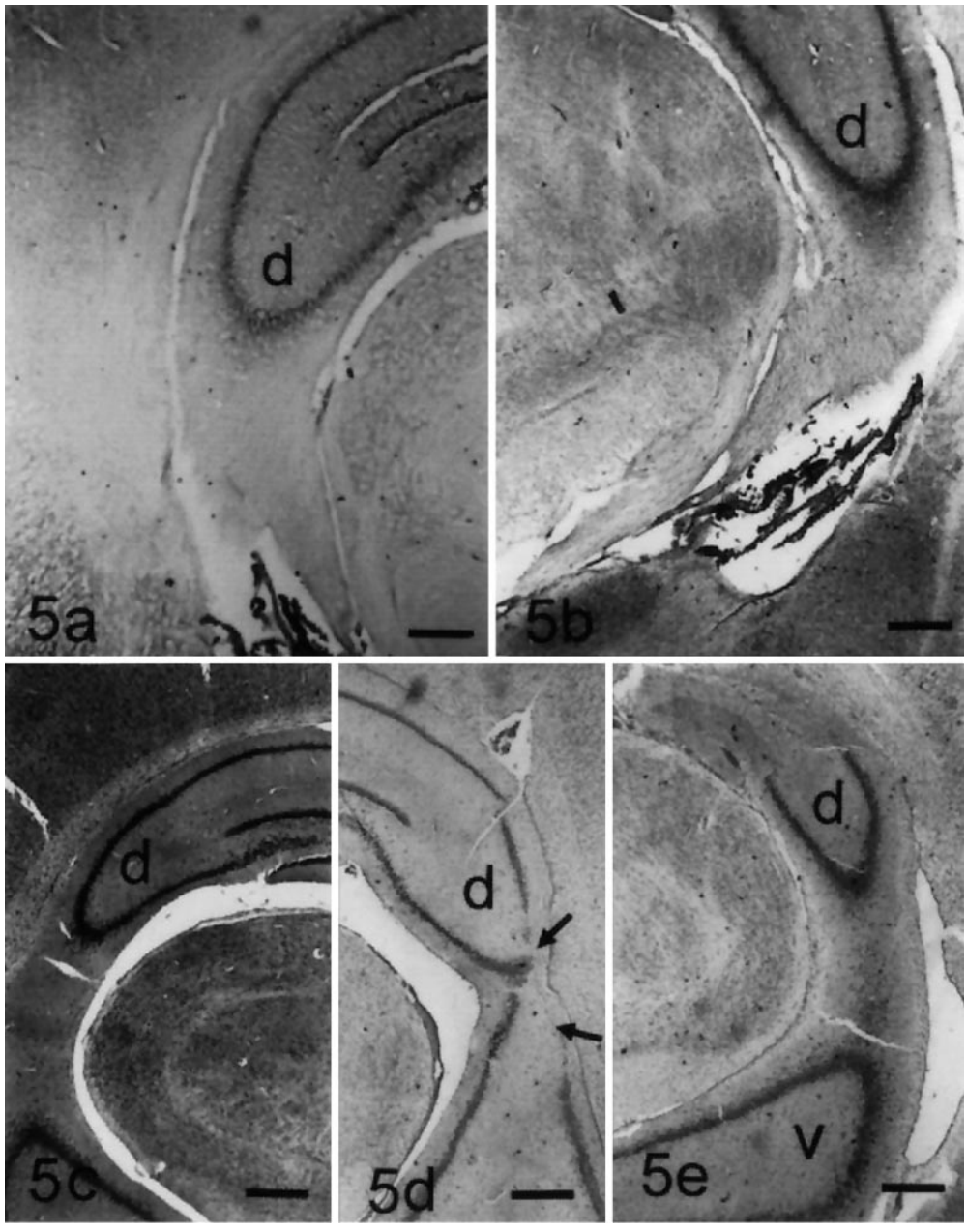

Fig. 5a–e Photomicrographs of Nissl-stained coronal sections through the brains of rats that received ibotenic acid or saline. **a** Neonatally lesioned animal. The ventral portion of the hippocampus is almost completely destroyed, whereas the dorsal part (*d*) is morphologically intact (level 4.30 mm posterior to bregma). *Bar*=130 µm. **b** Adult-lesioned rat. The excitotoxin generated damage of the ventral but not the dorsal (*d*) hippocampus (level approximately 4.40 mm posterior to bregma). *Bar*=130 µm. **c** Saline-treated rat (control): note that the entire hippocampus is undamaged (level 4.52 mm posterior to bregma) *Bar*= 150 µm. **d** Ibotenic acid treated rat with minor lesion. Neuronal loss is restricted to a small cell population (*arrows*). This animal was removed from data analysis (level approximately 4.75 mm posterior to bregma) *Bar*=130 µm. **e** Rat with ibotenic acid administration into the dorsal hippocampus (*d*). Note massive nerve cell loss and gliosis. Neurons belonging to the CA3 subregion are apparently undamaged. The ventral hippocampus (*v*) is not affected by the treatment (level 4.52 mm posterior to bregma). *Bar*=150 µm

The locations of the lesions were confirmed by careful histological inspection. Photomicrographs of the lesions of the dorsal and ventral hippocampus are seen in Fig. 5 and in Fig. 6. Nissl staining revealed massive neuronal loss and gliosis in the areas of neurotoxin injection. Sometimes, cavitations (Lipska and Weinberger 1995) were observed in close vicinity to the injection site which obviously resulted from tissue atrophy and ventricle enlargement. Animals with no visible or minor damage (Fig. 5d), unilateral lesion only, or tissue destruction affecting other than target structures of injection were not studied further (two animals in this study). Though there were considerable individual differences in the size of lesions (most probably due to either the presence or the absence of cavitations), the average volumes of the lesions were very similar for both groups (1.21±0.45 mm^3 for neonatally treated rats versus 1.24±0.57 mm^3 for adult-lesioned animals, both volume estimates being corrected for shrinkage during tissue processing).

Discussion

Our study clearly demonstrates that ibotenic acid lesion of the ventral hippocampus in neonatal rats dramatically altered social behaviour when the rats were tested at the age of 13 weeks. Total time spent in social interaction was significantly decreased in lesioned rats. Moreover, these rats had a higher level of aggressive components in behaviour (Fig. 1). In contrast, ibotenic acid lesion of the

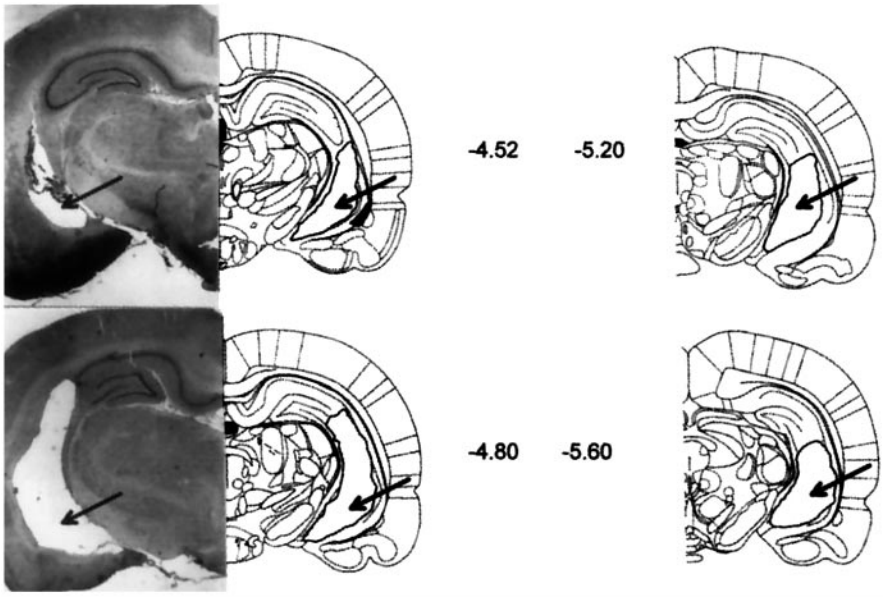

Fig. 6 Lesion boundaries defined as the area of neuronal absence and cavitation of coronal sections from brains of rats lesioned with ibotenic acid. *Arrows* indicate the lesion. Posterior coordinates relative to bregma

ventral and the dorsal hippocampus, respectively, in adult rats did not affect social behaviour when the animals were tested at the age of 18 weeks.

Maaswinkel et al. (1997) described three important aspects of the rodent hippocampus in social behaviour. It plays a role in the formation and application of social knowledge, it is important for behavioural sequencing and it is crucial for the decision about starting, stopping, or continuing a behaviour on the background of other demands resulting from the environment.

Numerous alterations in hippocampally damaged rats and mice have been described (Maaswinkel et al. 1997). Neonatal ibotenic acid lesions of the rat ventral hippocampus resulted in typical behavioural patterns, e.g. reduced prepulse inhibition, disruption of latent inhibition, behavioural hyperresponsiveness to dopaminergic stimulation and alterations in dopaminergic and glutamatergic neurotransmission (Lipska et al. 1992, 1995a,b; Lipska and Weinberger 1996; Wan et al. 1996; Wan and Corbett 1997; Grecksch et al. 1999), and therefore this lesion was suggested to be a relevant animal model reflecting aspects of schizophrenia (Lipska and Weinberger 1997). Interestingly, these alterations are detectable only after sexual maturity. This clearly suggests that disturbed neurodevelopmental processes rather than the lesion per se affect the behaviour of mature animals.

Sams-Dodd et al. (1997) investigated social behaviour in rats lesioned on postnatal day 7 (PD7). PD35 and PD65 lesioned rats spent significantly less time in active social interaction than sham-operated animals. However, the level of locomotor activity was only increased in lesioned PD65 rats. Obviously, alterations in social behaviour are independent of sexual maturity.

Our results (Fig. 1) are in good accordance with those obtained in the study by Sams-Dodd et al. (1997). Beside decreased time spent in social interaction, the ratio of non-aggressive to aggressive components was shifted towards increased aggressiveness. This shift is reliable because it was replicated in a set of subsequent experiments.

Sams-Dodd et al. (1997) reported on the increased levels of anxiety of lesioned rats and the authors concluded that deficits in social interaction might be indirectly caused by anxiety. To test this hypothesis, we examined the behaviour of neonatally lesioned rats in the elevated plus-maze, a widely used and validated animal model of anxiety (Pellow et al. 1985; Hogg 1996; Becker and Grecksch 1996; Rodgers 1997; Rodgers and Dalvi 1997). As shown in Fig. 4, we could not find significant differences between the experimental groups, suggesting that decreased time spent in social contact and increased aggressiveness are independent of anxiety. It is well known that results obtained in exploration tests of anxiety and social tests of anxiety are not unequivocal. Moreover, Lipska and Weinberger (1995b) found that rats with large ventral hippocampal lesions displayed enhanced spontaneous and amphetamine-induced locomotion as compared with controls at PD56, but not at PD35. Small lesions had no effect at any age. Thus, further experiments are needed to clarify whether the different results concerning are due to the different grades of hippocampal damage or, alternatively, a result of different experimental animal models of anxiety.

The hippocampus represents a heterogeneous structure. Its anatomical differentiation may result in functional differentiation. It has been shown that stimulation of the ventral hippocampus serves to facilitate biting attacks greatly, whereas dorsal hippocampal stimulation produces suppression of this response in cats (Siegel and Flynn 1968). Electrical kindling of both hippocampal structures resulted in different seizure scores and specific learning impairments (Becker et al. 1997). To find out whether the location of hippocampal damage and the stage of ontogenesis interfere in inducing shifts in social

behaviour, 8-week-old Sprague-Dawley rats were lesioned with ibotenic acid either in the ventral or the dorsal hippocampus and observed in the social interaction test when the animals were aged 18 weeks. As shown in Fig. 2 and Fig. 3, there were no differences between control and lesioned animals in the time spent in social interaction or the ratio of non-aggressive to aggressive behaviour. This clearly indicates that hippocampal damage per se did not alter the animals' social behaviour. Therefore, we favour neurodevelopmental disturbances leading to changes as found in our experiments. Further investigations aiming at pharmacological effects on shifted social behaviour of neonatal ibotenic acid lesioned rats are warranted.

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