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Early maternal deprivation and prepulse inhibition The role of the postdeprivation environment

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Abstract

Early postnatal maternal deprivation leads to a variety of biochemical and behavioural alterations in the offspring, some of which do not develop until adulthood, like deficits in prepulse inhibition. Since a number of these deficits are similar to abnormalities observed in schizophrenic patients, maternal deprivation has been proposed as an interesting model for schizophrenia. However, little is still known about the processes that determine these long-term consequences. Previous experiments showed that the strain of rats and the deprivation procedure are important factors. In the present set of experiments, we focussed on the postdeprivation period. We showed that rearing normal Wistar rats in social isolation from weaning disrupts prepulse inhibition. However, if maternally deprived Wistar rats were reared in social isolation, the prepulse inhibition was normal. We further showed that if only half of the litters were maternally deprived at postnatal day 9, the animals had only a small disruption in prepulse inhibition compared to animals that came from litters where all the animals were deprived. In a final experiment, we crossfostered maternally deprived mothers to nondeprived pups and vice versa. This experiment showed that both the nondeprived pups raised by a deprived mother and the deprived pups raised by a nondeprived mother had small deficits in prepulse inhibition. Taken together, these data clearly show that the postdeprivation period is of crucial importance for the development of prepulse inhibition deficits in maternally deprived rats. We present a working model in order to explain the long-term behavioural consequences of maternal deprivation.

Keywords: Prepulse inhibition; Schizophrenia; Maternal deprivation; Isolation rearing; Stress

1. Introduction

During a specific period in early development, rats show a greatly reduced sensitivity of the hypothalamic–pituitary–adrenal (HPA) axis. This period, roughly extending from postnatal day (PND) 4 to 14, is generally referred to as the stress hyporesponsive period (SHRP) and is characterized by a diminished ACTH and corticosterone response to most stressors, as well as an adrenal insensitivity to ACTH (Rosenfeld et al., 1991; Suchecki et al., 1993; Sapolsky and Meaney, 1986). This SHRP is generally thought to represent a protective mechanism to prevent the detrimental effects of increased levels of corticosterone on the brain (de Kloet et al., 1988). One way of overcoming the SHRP is by applying a severe stressor, such as prolonged maternal deprivation (Levine, 1994). Separating pups from their mother for 8 or 24 h induces a strong increase in corticosterone both under basal conditions, as well as after novelty stress (Stanton et al., 1988). Interestingly, the increase in baseline corticosterone seems to persist for a prolonged period and is even present in adult rats (Rots et al., 1996). In line with these finding, several other long-term alterations have been reported after neonatal maternal deprivation. These include an increase in baseline ACTH (Rots et al., 1996) and a decrease in the number of glucocorticoid and mineralocorticoid receptors in the hippocampus (Sutanto et al., 1996).

Recently, we and others have shown that early maternal deprivation also induces a number of abnormalities related to schizophrenia. Thus, maternally deprived rats (deprived from their mothers for a single period of 24 h, shortly after birth, typically PND 9) have a diminished prepulse inhibition (Ellenbroek and Cools, 2000; Ellenbroek et al., 1998) and latent inhibition (Ellenbroek and Cools, 1995), as well as an increased sensitivity to apomorphine (Ellenbroek and Cools, 1995). This latter increase in sensitivity is accompanied by an increase in tyrosine hydroxylase mRNA in the substantia nigra (Rots et al., 1996). Moreover, reductions in

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P_{50} gating and startle habituation have also been found (Ellenbroek et al., in preparation). These findings have led to the notion that maternal deprivation might represent an interesting new animal model for schizophrenia (Ellenbroek et al., 2000; Lipska and Weinberger, 2000), especially since the effects on prepulse inhibition develop after puberty and are sensitive to antipsychotics such as haloperidol and quetiapine. It is, at present, unclear how these behavioural changes develop, although genetic factors are known to play an important role, as well as the deprivation procedure itself (Ellenbroek and Cools, 2000). However, given the fact that these effects are not yet observed at PND 35 suggests that certain long-term processes are set in motion by the early deprivation, possibly initiated by the acute effects on the HPA axis. This raises the question of whether these consequences are inevitable or whether manipulations after the deprivation period may somehow influence the long-term consequence. It is well known that environmental manipulations later in the development of rats may influence prepulse inhibition. For instance, rearing rats in isolation from others (Geyer et al., 1993; Wilkinson et al., 1994; Varty and Higgins, 1995) or placing animals on a grid floor after weaning (Weiss et al., 1999) can lead to reductions in prepulse inhibition. The present paper investigates the effects of manipulations of the post deprivation period on prepulse inhibition. In Experiment 1, we first tried to replicate the original finding of maternal deprivation on PND 9 on prepulse inhibition and extended this by also looking at deprivation at the end of the SHRP (i.e. PND 13). In the second experiment, we investigated the effects of isolation rearing alone and in combination with maternal deprivation. Experiments 3 and 4 were aimed at investigating the role of the mother. It is important to realise that maternal deprivation not only deprives rat pups from their mother, but also mothers from her pups. This 24-h isolation of the mother may very well lead to alterations in maternal behaviour and possibly milk production, which might influence the deprivational effect. Therefore, in Experiment 3, we applied the so-called half litter procedure (i.e. only half of the litters were deprived, the other half remained with the mother), and in Experiment 4, we applied a crossfostering procedure immediately after the deprivation. The results clearly show that the alterations in prepulse inhibition are not inevitable consequences of the maternal deprivation but also depend on the environment after the deprivation period. Moreover, the data show that the mother plays a crucial role in this period.

2. Material and methods

2.1. Animals

Male and nulliparous female Wistar rats, 3 months old, were put together in standard Macrolon cages with sawdust ($26 \times 42 \times 15$ cm) in temperature-controlled rooms (23 ± 1 °C). The rats were on a standard 12-h light/dark cycle with light on from 07:00 to 19:00 h, with water and food freely available. Two weeks later, the males were removed from the cages and the females were checked twice daily for delivery (08:00 and 17:00 h). The day of delivery was denoted as PND 0. On PND 1, the litters were weighed and culled to six males and two females. In all experimental groups, male rats of at least four different litters were used in order to reduce litter effects. Rats were only used once. All experiments were done in accordance with (inter)national regulations and institutional guidelines.

2.2. Maternal deprivation

Maternal deprivation took place on PND 9 according to our standard procedure (Ellenbroek et al., 1998), except in Experiment 1, where part of the litters were deprived at PND 13. In brief, the mothers were removed at 10:00 h, after which the pups were weighed and returned to their home cage. They remained in their home cage at room temperature for 24 h. On PND 10, the pups were weighed again, and the mothers were returned to their cages. The mothers of the control litters were briefly removed from their home cages, and the pups were weighed both on PND 9 and PND 10. Weaning took place at PND 21, where rats were normally housed in groups of three males. The two females were housed together but were not used for the present experiments. Prepulse inhibition testing was performed on PND 69.

2.3. Prepulse inhibition

On PND 69, all animals were subjected to the prepulse inhibition test. The animals were transported to a room adjacent to the startle chamber room and left undisturbed for at least 30 min. In the prepulse inhibition paradigm, four standard startle chambers of San Diego Instruments were used. The startle chamber consisted of a Plexiglas tube (diameter 8.2 cm, length 25 cm), placed in a sound-attenuated chamber, in which the rats were individually placed. The tube was mounted on a plastic frame, under which a piezoelectric accelerometer was mounted, which recorded and transduced the motion of the tube. After the rats were placed into the chamber, they were allowed to habituate for a period of 5 min during which a 70-dB[A] background white noise was present. After this period, the rats received 10 startle trials, 10 no-stimulus trials and 30 prepulse inhibition trials. The intertrial interval was between 10 and 20 s, and the total session lasted about 17 min. The startle trial consisted of a single 120-dB[A] white noise burst lasting 20 ms. The prepulse inhibition trials consisted of a prepulse (20-ms burst of white noise with intensities of 73, 75 or 80 db[A]), followed 100 ms later by a startle stimulus (120-dB[A], 20-ms white noise). Each of the three prepulse trials (73, 75 and 80 dB[A]) were presented 10 times. During the no-stimulus trial, no stimulus is presented, but the movement

of the rat is scored. This represents a control trial for detecting differences in overall activity. The 50 different trials were presented pseudorandomly, ensuring that each trial was presented 10 times and that no two consecutive trials were identical. The resulting movement of the rat in the startle chamber was measured during 100 ms after startle stimulus onset (sampling frequency 1 kHz), rectified, amplified and fed into a computer, which calculated the maximal response over the 100-ms period. Basal startle amplitude was determined as the mean amplitude of the 10 startle trials. Prepulse inhibition was calculated according to the formula $100-100\%\times(PPx/P120)$, in which PPx is the mean of the 10 prepulse inhibition trials (PP73, PP75 or PP80) and P120 is the basal startle amplitude.

2.4. Experiment 1

In Experiment 1, prepulse inhibition was measured in control rats (Ctrl, $n=17$) and was compared with those of the rats that were subjected to maternal deprivation on PND 9 (MD9, $n=20$) and rats that were deprived at PND 13 (MD13, $n=12$).

2.5. Experiment 2

In Experiment 2, half of the control rats and half of the maternally deprived rats were placed in groups of three males at weaning, whereas the other half were placed in identical cages but socially isolated from their littermates. This led to four groups of rats: C/S: control rats, socially reared ($n=16$); MD/S: maternally deprived rats, socially reared ($n=16$); C/I: control rats, reared in isolation ($n=9$); MD/I: maternally deprived rats, reared in isolation ($n=9$).

2.6. Experiment 3

In Experiment 3, four litters were subjected to the so-called half litter procedure. This implies that at PND 9, all rats were removed from the mother and were weighed, but half of the litters (i.e. three males and one female) were returned to the mother immediately after weighing. The others were placed in another cage, with two hands full of sawdust from the home cage. On PND 10, all pups were weighed again and returned to the mothers. This led to four groups: Ctrl: control rats ($n=16$); MD9: maternally deprived rats ($n=16$); ISO: the rats from the half litter group that were deprived for 24 h ($n=10$); NISO: the rats from the half litter group that remained with the mother ($n=9$).

2.7. Experiment 4

In Experiment 4, rats were subjected to maternal deprivation on PND 9. On PND 10, half of the control mothers (i.e. those that were with their own pups throughout the deprivation period) were crossfostered to deprived pups, and the deprived mothers (i.e. those that were deprived from pups on PND 9) were crossfostered to the control pups. This again led to four different groups: Ctrl: control rats ($n=16$); MD9: maternally deprived rats ($n=16$); CMDP: deprived pups raised by control mothers ($n=16$); DMCP: control pups raised by deprived mothers ($n=16$).

2.8. Statistics

Differences in basal startle amplitude were analysed by an analysis of variance (ANOVA). The overall effect on prepulse inhibition was determined by an ANOVA with repeated measures for the different prepulse intensities. In case of a significant effect, post hoc Duncan tests were performed to evaluate the statistical differences between the groups.

3. Results

3.1. Experiment 1

Maternal deprivation did not influence basal startle amplitude at PND 9 or at PND 13 [see Fig. 1A, $F(2,46)=0.87$; $P>.42$]. Maternal deprivation did, however, induce a sig-

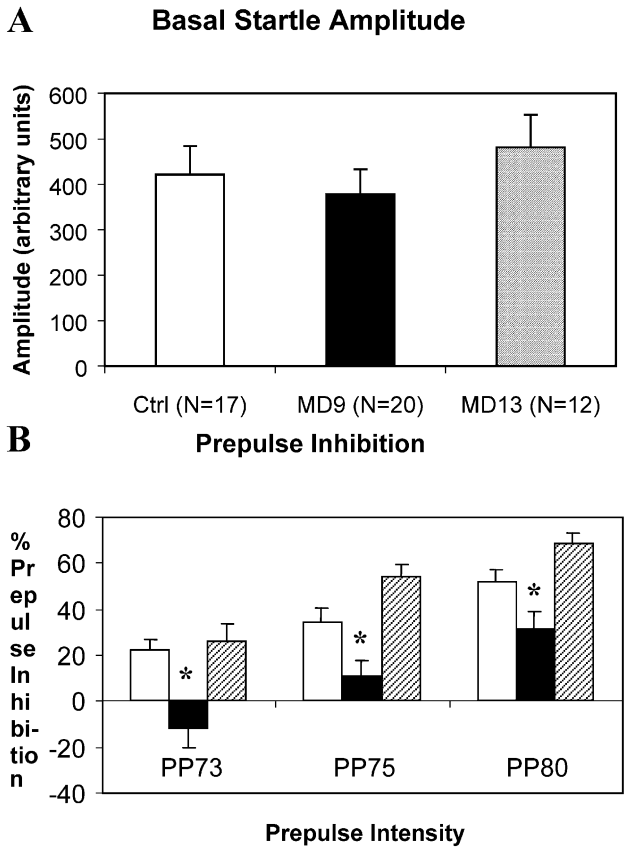

Fig. 1. (A) Basal startle amplitude in arbitrary units; (B) prepulse inhibition (calculated according to the formula described in Section 2) of rats from Experiment 1. Abbreviations: Ctrl: control rats; MD9: rats maternally deprived on PND 9; MD13: rats maternally deprived at PND 13. (*) Significantly different from Ctrl.

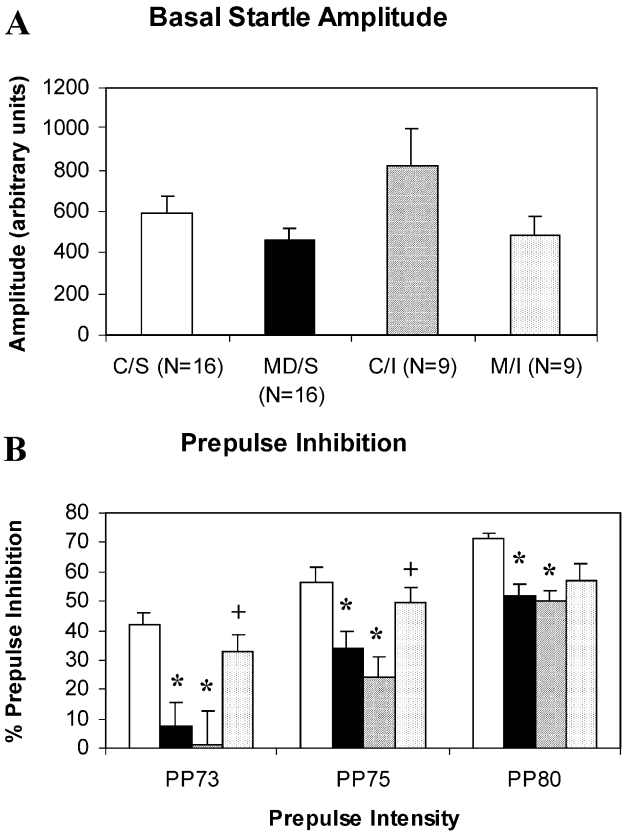

Fig. 2. (A) Basal startle amplitude in arbitrary units; (B) prepulse inhibition (calculated according to the formula described in Section 2) of rats from Experiment 2. Abbreviations C/S: control rats, socially reared; MD/S: maternally deprived rats, socially reared; C/I: control rats, reared in isolation; MD/I: maternally deprived rats, reared in isolation. (*) Significantly different from C/S. (+) Significantly different from MD/S.

nificant alteration in prepulse inhibition [$F(2,46)=11.0$; $P<.001$]. Post hoc analysis showed that this was entirely due to the reduction in prepulse inhibition in the animals deprived at PND 9. As is evident in Fig. 1B, deprivation on PND 13 had no effect on prepulse inhibition.

3.2. Experiment 2

The results are depicted in Fig. 2 and were analysed with a two-factor ANOVA with early manipulation (maternal deprivation vs. control) and rearing condition (group housed vs. isolated) as between-subjects parameters. This analysis showed a significant effect of early manipulation on basal startle amplitude [$F(1,46)=6.2$; $P<.02$] but not of rearing condition [$F(2,46)=1.8$; $P>.18$]. Likewise, the interaction was also not significant [$F(1,46)=1.2$; $P>.27$]. Post hoc analysis, however, did not show a significant difference between the individual groups, though there was a tendency for rats in the C/I group to have a higher basal startle amplitude than the rats in the MD/S group.

The effects with respect to prepulse inhibition showed no overall effect of early manipulation [$F(2,46)=0.2$; $P>.65$] nor of rearing condition [$F(2,46)=2.6$; $P>.12$]. There was, however, a highly significant interaction between the two factors [$F(2,46)=22.3$; $P<.001$]. Post hoc analysis showed that the group-reared maternally deprived rats, as well as the isolation-reared control rats, differed significantly from the group-reared control animals (see Fig. 2B). Moreover, there was a significant difference between the group-housed maternally deprived animals and the isolation-reared maternally deprived rats. Put differently, the subsequent isolation rearing reversed the effects of maternal deprivation.

3.3. Experiment 3

Fig. 3 shows the results from the half litter deprivation procedure. ANOVA showed that there was a difference in basal startle amplitude, which almost reached significance [$F(3,47)=2.63$; $P=.06$]. Post hoc analysis showed that this was due to an almost significant difference between the control group and the ISO group (i.e. animal that were deprived in the half litter group). With respect to prepulse inhibition, the ANOVA showed a very significant group effect [$F(3,47)=8.2$; $P<.001$]. Post hoc analysis showed

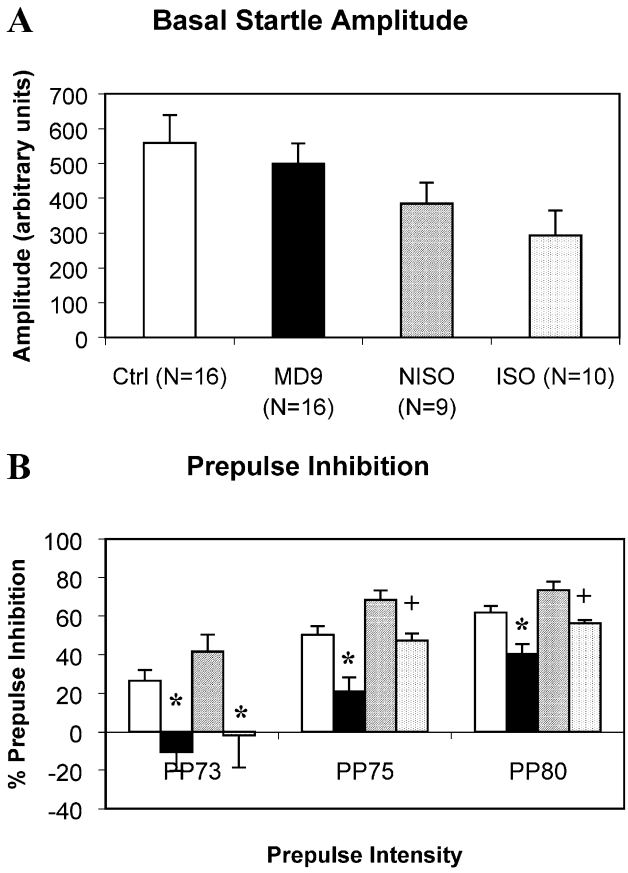

Fig. 3. (A) Basal startle amplitude in arbitrary units; (B) prepulse inhibition (calculated according to the formula described in Section 2) of rats from Experiment 3. Abbreviations Ctrl: control rats; MD9: maternally deprived rats; ISO: the rats from the half litter group that were deprived for 24 h; NISO: the rats from the half litter group that remained with the mother. (*) Significantly different from Ctrl.

that the MD9 group had a significantly reduced prepulse inhibition in comparison to control rats. The ISO group also differed significantly from the control animals, but only at the lowest prepulse intensity.

3.4. Experiment 4

The results of Experiment 4 are displayed in Fig. 4. In agreement with the other experiments, there were no significant effects on basal startle amplitude. This was confirmed using an ANOVA with two between-subjects factors: mother (control vs. deprived) and pups (control vs. deprived). Neither factor significantly influenced basal startle amplitude [mother $F(1,60)=0.05$; $P>.8$; pup: $F(1,60)=2.34$; $P>.13$]. On the other hand, the interaction factor was significant [$F(1,60)=6.36$; $P<.02$]. Inspection of Fig. 4A shows the presence of deprived pups reduced startle amplitude in control rats (the Ctrl group differed significantly from the CMDP group), whereas there were no differences between the MD9 and the DMCP groups.

When analysing prepulse inhibition, we found that both the factor mother [$F(1,60)=4.42$; $P<.04$] and the factor pup [$F(1,60)=7.5$; $P<.01$] were significant, as well as interaction between these two factors [$F(1,60)=4.1$; $P<.05$]. Post hoc analysis showed that the MD9 and the DMCP group differed significantly from controls at all prepulse intensities. Moreover, whereas the CMDP group differed significantly from the Ctrl group at the lowest prepulse intensity, there were significant differences between the CMDP group and the MD9 group at the two highest prepulse intensities.

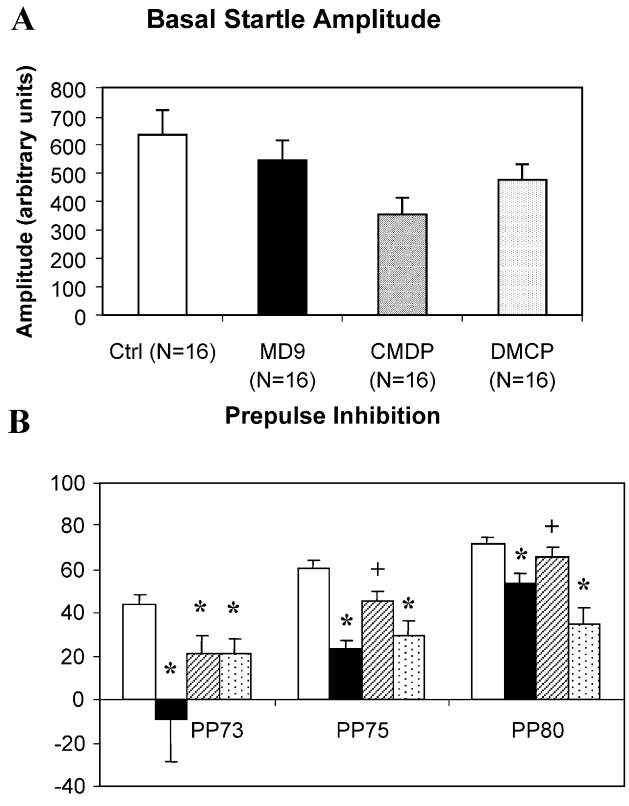

Fig. 4. (A) Basal startle amplitude in arbitrary units; (B) prepulse inhibition (calculated according to the formula described in Section 2) of rats from Experiment 4. Abbreviations Ctrl: control rats; MD9: maternally deprived rats; CMDP: Deprived pups raised by control mothers; DMCP: control pups raised by deprived mothers. (*) Significantly different from Ctrl.

4. Discussion

It has previously been reported that early maternal deprivation can disrupt prepulse inhibition in adult rats depending on the day of deprivation (Ellenbroek and Cools, 2000; Ellenbroek et al., 1998). The present data confirm and extend these findings by showing that prepulse inhibition was disrupted when deprivation took place at PND 9, but that it was intact when rats were deprived at PND 13. Together with previous results, these data show that prepulse inhibition is most severely affected when deprivation takes place around PND 6 to PND 9, i.e. right in the middle of the SHRP. It is important to realise that maternal deprivation at PND 6 to PND 9 not only eliminates general maternal care (like licking) but also food intake. Moreover, it affects the body temperature of the pups, since these animals have no fur yet and cannot regulate their own body temperature. It has been shown earlier that maternal deprivation at room temperature (20 °C) leads to an increased sensitivity to amphetamine, which is not seen when the pups are kept at 34 °C (Zimmerberg and Shartrand, 1992). On PND 13, rats are much more mature, and they can control their own body temperature much better due to their fur. Though this may explain the lack of effect on prepulse inhibition in these animals, it cannot explain the relatively small effects observed after deprivation on PND3 (Ellenbroek et al., 1998). However, it may (in part) also explain the lack of effect on prepulse inhibition observed in a recent paper (Lehmann et al., 2000), since in contrast to the present study, these authors kept the pups in an incubator during the deprivation period.

The present data show that factors beyond the deprivation period can also influence the behavioural outcome. Thus, when only half of the pups in each litter were deprived, and, therefore, the mother had pups to nurse during the deprivation period, the deprived pups were much less affected, in spite of the fact that they had experienced an identical 24-h period of deprivation (see Fig. 3). Indeed, these pups only showed a reduction in prepulse inhibition at the lowest prepulse inhibition intensity and had prepulse inhibition levels in-between the controls and the maternally deprived rats. This was also seen in their body weight at weaning: the Ctrl and NISO groups had the highest body weight (Ctrl: 58.2±2.2 g.; NISO=57.3±2.6 g.), the MD9 the lowest (43.9±1.1 g.) and the ISO group in-between (51.9±1.8 g.). This clearly suggests that the behaviour of the mother (and possibly her milk production) is also affected by the deprivation period.

Experiment 4 further supports the idea that the final outcome of the maternal deprivation procedure depends both on the mother, as well as on her pups. In this experiment, we have performed crossfostering at the end of the deprivation period. We had already shown that crossfostering at PND 10 had no effect on prepulse inhibition in normal control animals (unpublished results). This crossfostering procedure allowed us to tease out the relative contribution of the deprivation of the mother, and the deprivation of the pups, since one group (CMDP) consisted of pups that had been deprived in an identical way as the MD9 group but had obtained a nondeprived mother at the end of the deprivation period. On the other hand, the pups of the DMCP group had not been deprived like the Ctrl rats but obtained a deprived mother at PND 10. The data showed that both factors were important. Indeed, inspection of Fig. 4B shows that at the lowest prepulse intensity both the CMDP and the DMCP group had a significantly reduced prepulse inhibition, which did not differ significantly from the MD9 group. In other words, even rats that had been with a mother during the entire period prior to weaning could show reductions in prepulse inhibition when they were nursed (from PND 10 on) by a mother that had been deprived for 24 h. This effect was also seen at the highest prepulse intensity. It is, at present, unclear in which way deprived mothers differ from nondeprived mothers. Further analysis of the maternal behaviour will be necessary to investigate this. It has been reported repeatedly that maternal behaviour may direct the behaviour and the make-up of the brain and the endocrine system in adulthood (Liu et al., 1997, 2000). In addition, there was a difference between the MD9 and the CMDP group, which reached significance at the highest two prepulse intensities, which shows that a crossfostering deprived pups to a nondeprived mother reduced the deficit in prepulse inhibition.

The results of Experiment 2 also showed that changes in the postdeprivation period can influence the behavioural outcome of maternal deprivation. First, the data show that socially isolating normal control rats from weaning disrupted prepulse inhibition, a finding in line with many other publications (Geyer et al., 1993; Wilkinson et al., 1994; Varty and Higgins, 1995). Moreover, maternal deprivation at PND 9, again disrupted prepulse inhibition, in line with the other experiments (Ellenbroek and Cools, 2000; Ellenbroek et al., 1998). However, when the two procedures were combined, no reduction in prepulse inhibition was observed. Indeed, the disruption induced by maternal deprivation at the lowest two prepulse intensities, was significantly reversed by subsequent rearing in isolation. Even though it is in line with the general results of the present paper, that alteration in the environment after the deprivation period may influence the behavioural outcome, it is nonetheless surprising. Both maternal deprivation and isolation rearing have been proposed as animal models for schizophrenia (Ellenbroek and Cools, 1998; Ellenbroek et al., 2000; Geyer et al., 1993). However, some differences have also been observed between the two models. First, maternally deprived Wistar rats show a reduced locomotor and an increased stereotypy response to apomorphine (Ellenbroek and Cools, 1995, 1998). Isolation-reared animals, on the other hand, show the opposite picture, an increased sensitivity to the locomotor stimulating properties of dopamine agonists and a reduced sensitivity to apomorphine induced stereotypy (Jones et al., 1990). Locomotor activity is classically attributed to increases in dopamine in the nucleus accumbens (Pijnenburg et al., 1976), whereas stereotypy is attributed to the neostriatum (Broekkamp et al., 1975). This suggests that isolation rearing leads to an increase in dopamine transmission within the nucleus accumbens, whereas maternal deprivation leads to increases within the neostriatum. Microdialysis studies have indeed shown that isolation rearing is accompanied by an increased dopamine transmission within the nucleus accumbens (Wilkinson et al., 1994). Moreover, maternal deprivation leads to a disruption in latent inhibition using the conditioned taste aversion paradigm (Ellenbroek and Cools, 1995), which is also seen after amphetamine microinjections into the neostriatum (Ellenbroek et al., 1997). Moreover, whereas maternal deprivation leads to alterations in the HPA axis and the stress sensitivity (see above), no such differences were seen in isolation-reared rats (Holson et al., 1988, 1991). In fact, smaller increases in plasma corticosterone were observed in isolation-reared rats placed on an open field compared to group-housed rats (Gentsch et al., 1981). It is tempting to speculate that the mirror image between isolation rearing and maternal deprivation with respect to the dopaminergic systems and the stress responsiveness might have counteracted the effects on prepulse inhibition. However, more research is necessary to investigate this hypothesis.

Taken all these data together, we can conclude that the long-term consequences of maternal deprivation depend not only on the date of deprivation and the deprivation procedure itself, but also strongly depend upon the postdeprivation environment. Although, at present, it seems impossible to explain how these long-term alterations may come about, it is tempting to speculate that they may somehow be related to the alterations in the HPA axis. As discussed in Section 1, one of the first effects of maternal deprivation is an increase in basal levels of ACTH and corticosterone, as well as an increase in the response of the HPA axis to stress, which may persist into adulthood (Stanton et al., 1988; Rots et al., 1996; Sutanto et al., 1996). This implies that stressors, which would normally produce a small short-lasting increase in corticosterone, have a much more profound effect in maternally deprived rats. Since corticosterone has detrimental effects on the brain (Bohn, 1984), and especially on the hippocampal formation (Gould, 1994), one might speculate that the deficits in prepulse inhibition may be due to the long-lasting influence of corticosterone on the hippocampus. This would be in line with the wealth of data implicating the hippocampal formation in modulation prepulse inhibition (Caine et al., 1991, 1992; Koch, 1999; Lipska et al., 1995).

This model (see Fig. 5) proposes that if maternally deprived animals are reared in a relatively stressful envir-

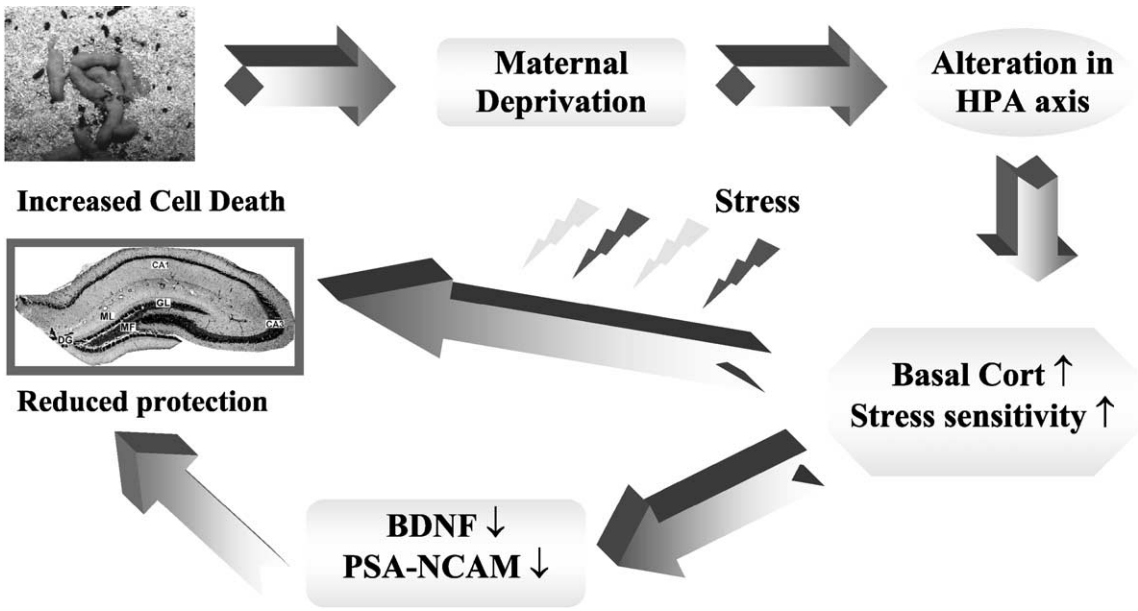

Fig. 5. A working model to explain the development of long-term abnormalities after early maternal deprivation. See text for further explanation.

onment, large increases in corticosterone will repeatedly be produced, which might produce extensive damage to the brain, and especially to the hippocampus. This is all the more important as we have recently found that maternal deprivation leads to significant reductions in hippocampal levels of polysialylated neural cell adhesion molecule (PSA-NCAM), brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2) (Foley et al., 2000; Riva et al., 2000). These factors are known to play a protective role in the central nervous system (Goutan et al., 1998; Jucker et al., 1995). In other words, maternal deprivation leads both to an increase in neurotoxic substances (corticosterone) and to a reduction in neuroprotective substances (PSA-NCAM, BDNF and FGF-2), thereby making the hippocampus particularly vulnerable.

Although the model displayed in Fig. 5 is no more than a working hypothesis, it would explain why the effects of maternal deprivation (on prepulse inhibition) are not seen until after puberty, for it requires long-lasting increases in corticosterone before appreciable damage to the hippocampus is achieved (Sapolsky, 1994). Moreover, it would explain why alterations in the postdeprivational period might prevent the subsequent development of prepulse inhibition deficits. In fact, any manipulation that might make the environment less stressful should have a protective effect. Thus, replacing a deprived mother with a nondeprived mother (Experiments 3 and 4) would probably lead to a less stressful environment. Moreover, the fact that isolation rearing leads to a down-regulation of the HPA axis sensitivity (Gentsch et al., 1981) might explain why maternally deprived rats subsequently reared in isolation might have less prepulse inhibition deficit than maternally deprived rats reared in a social environment.

In conclusion, the present experiments were designed to investigate whether the long-term deficits in prepulse inhibition observed after early maternal deprivation could be altered by changing the postdeprivation environment. The results showed that this is indeed the case. Thus, the prepulse inhibition deficits were reversed by (1) subsequent rearing in isolation, (2) depriving only half of the litters and (3) crossfostering the deprived rats to a nondeprived mother. Moreover, we presented a working model based on the findings that maternal deprivation leads to increases in the HPA axis and decreases in a number of neurotrophic factors.

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