MATERNAL SEPARATION REDUCES LATENT INHIBITION IN THE CONDITIONED TASTE AVERSION PARADIGM

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SUMMARY

Recent advances in the study of cognitive functioning and information processing in schizophrenic patients have made it clear that these patients suffer from disturbances in selective attention, which can be measured, among others with the latent inhibition paradigm. Given the fact that there is increasing evidence that schizophrenia is a neurodevelopmental disorder and that early maternal separation leads to clear neurodevelopmental disturbances in rats we studied the effects of early maternal separation on the development of latent inhibition using the conditioned taste aversion paradigm. The results show that early maternal separation enhances the susceptibility of rats for the dopamine agonist apomorphine and at the same time disrupts the development of latent inhibition. Given the evidence of a critical role for the hippocampus in latent inhibition and the fact that this brain structure seems to be particularly sensitive to disturbances in the early postnatal phase, the early maternal separation paradigm may represent an interesting animal model for studying information processing disturbances in schizophrenia.

KEYWORDS: Animal models, Apomorphine, Gnawing, Information Processing, Latent Inhibition, Maternal Separation, Schizophrenia.

INTRODUCTION

The development of animal models for schizophrenia has gained momentum with the introduction of models based on information processing deficits (1). It has been argued that these cognitive models are more closely related to the brain structures which are thought to be dysfunctioning in schizophrenic patients (2). Irrespective of this, these models are promising since they can measure the same features in humans and rats. Among these models are prepulse inhibition (3), P_{50} gating (4) and latent inhibition (5). The most important question that remains is how to disrupt the information processing in such a way in rats that it most closely resembles schizophrenia. One obvious way is to use drugs such as amphetamine (or other dopaminergic

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drugs) or phencyclidine. These drugs are known to disrupt certain aspects of information processing. Another strategy is to try and manipulate the development of the nervous system. There is quite some evidence that schizophrenia may be a developmental disorder (6). Indeed early social isolation (immediately after weaning) has been shown to disrupt prepulse inhibition (7). Another technique for inducing developmental disturbances is early maternal separation, i.e. removing the mother from her litter (8). Several authors have shown that early maternal separation affects (among others) the dopaminergic sensitivity of rats (9,10). Since we have recently found that apomorphine sensitivity was negatively correlated with latent inhibition (11), we studied the effects of early maternal separation on latent inhibition as well as on dopaminergic sensitivity. Latent inhibition (LI) refers to the detrimental effect of stimulus preexposure on subsequent conditioning of that stimulus. This implies that LI can be measured in many different learning paradigms. We decided to use the conditioned taste aversion paradigm, because of its simplicity, and because LI can be easily demonstrated in this paradigm (12).

MATERIALS AND METHODS

In order to study the effect of early maternal separation we used eleven pregnant female Wistar rats. After the litters were born we did not reduce them to a standard size, because they were all of comparable size (10 to 12 rats per litter). Five of these litters were used as controls whereas the other six formed the experimental group. The mothers were removed from these experimental litters for 24 h at day 10 after birth. The litters remained in their home cage and the temperature of the litters was controlled to be 22 to 24 °C. After 24 h the mothers were returned to their litters, and all litters were left undisturbed until weaning at 28 days. At weaning the rats were placed in cages in groups of 2 to 3 rats of equal gender until they were tested at day 60 after birth.

For the latent inhibition experiment 20 control rats and 20 maternal deprived rats were used. Both groups were further subdivided into a preexposed group and a nonpreexposed group, each consisting of 10 rats. All rats were water deprived 24 hours before the start of the experiment. On the first day of the experiment the preexposed groups received a drinking bottle filled with 50 ml of a 5% sucrose solution on the lid of their homecage. The nonpreexposed group received a bottle with 50 ml of tab water on the lid of their homecage. The bottles were left in place for 30 minutes after which the volume consumed was measured. This procedure was repeated on day 2 and day 3. On day 4 all rats received 50 ml of a 5% sucrose solution for 30 minutes. After this each rat was intraperitoneally injected with 50 mg/kg LiCl (5 ml/kg). On day 5, the test day, each rat received one bottle with 50 ml tab water and one bottle with 50 ml 5% sucrose solution. After 30 minutes the bottles were again removed and the total consumption as well as the percentage of sucrose consumed was determined.

For the apomorphine gnawing test 18 control rats and 14 maternally deprived rats were used. The animals were individually housed three days before the experiment. On the day of the experiment the rats were subcutaneously injected with 1.5 mg/kg apomorphine-HCl (Brocades, ACF) and immediately placed in the so-called gnawing box (13). This box closely resembles the gnawing box first described by Ljungberg & Ungerstedt (14). It consists of a square holeboard

(69 x 69 cm) with a central cubicle. Each of the 32 holes is surrounded by five concentric ridges, on which the animals could gnaw. The box is equipped with a number of photoelectric cells (to measure hole-dipping, (locomotor) activity and time spent in the corner), and with a microphone. The gnawing of the rat which nearly always occurred on the ridges around the holes, caused a characteristic vibration which was detected by the microphone, amplified, converted and fed into a computer. The rats were allowed into the gnawing box for 45 minutes after which the number of gnawing counts was calculated.

The statistical comparison between maternally deprived and control rats was done with a analysis of variance, and where appropriate with a post hoc Duncan test.

RESULTS

The results of the latent inhibition experiment are shown in figure 1. One rat in the preexposed group of the maternally deprived rats had to be discarded because of leakage of the bottle. In the control group both conditioned taste aversion and latent inhibition occurred. Thus the nonpreexposed rats had a clear aversion to sucrose (less than 20% of the total consumption on the test day). Latent inhibition occurred since the preexposed rats drank significantly more sucrose than the nonpreexposed rats, in other words prior preexposure reduced the conditioned taste aversion.

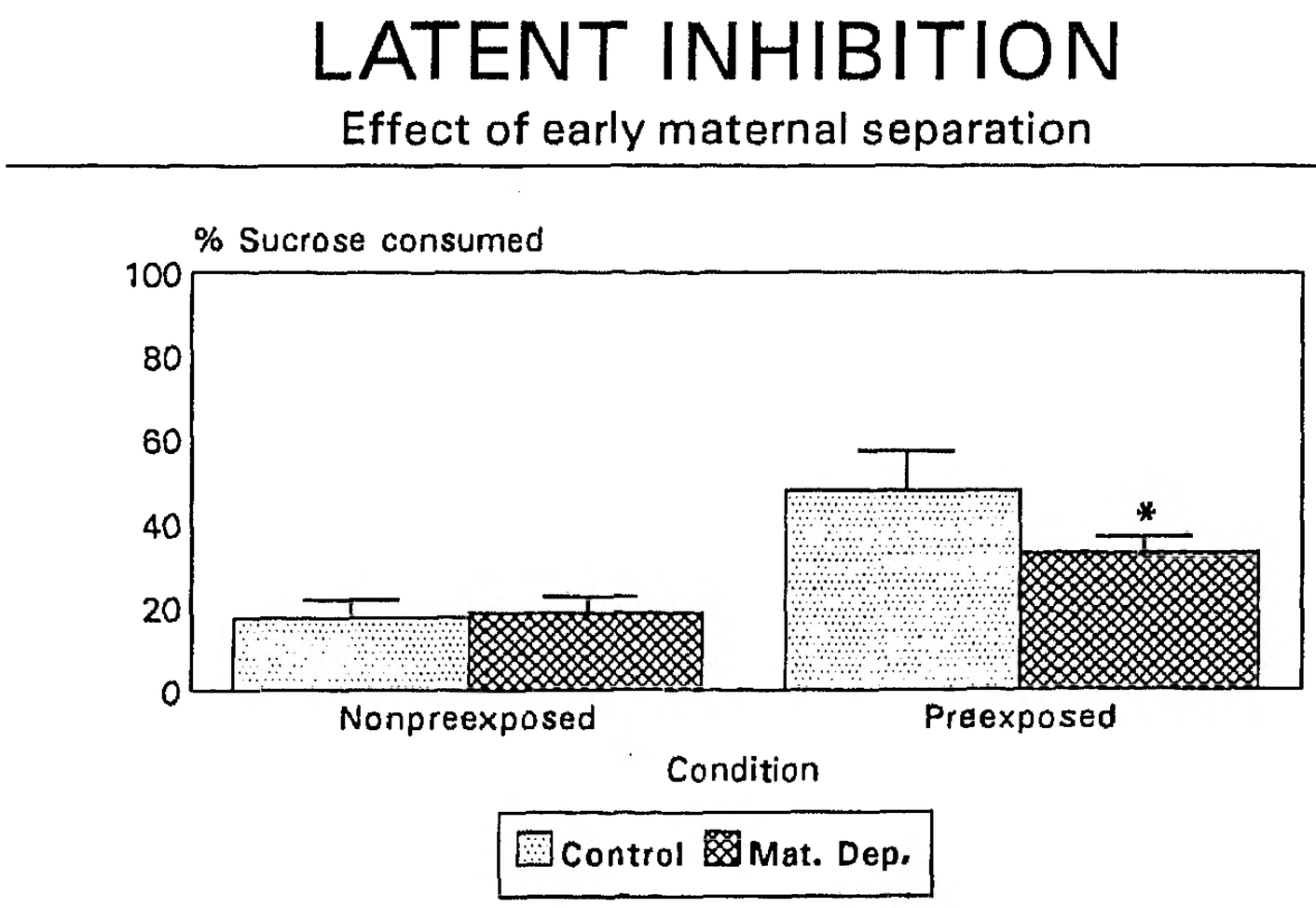

*Figure 1: The effects of early maternal separation on latent inhibition of the conditioned taste aversion paradigm. Mat Dep : maternal separation. * $p < 0.001$ maternal separation vs control.*

In the maternally deprived group conditioned taste aversion occurred (i.e. the nonpreexpo-

sed group drank very little sucrose) but there was much less latent inhibition. This was confirmed by a significant overall ANOVA ($F_{(3,35)}=10.93$; $p < 0.001$). Post hoc Duncan test showed that the maternally deprived preexposed group drank significantly less sucrose than the control preexposed group, although both groups drank significantly more than the nonpreexposed groups. There were no differences in the total intake of the different groups (data not shown).

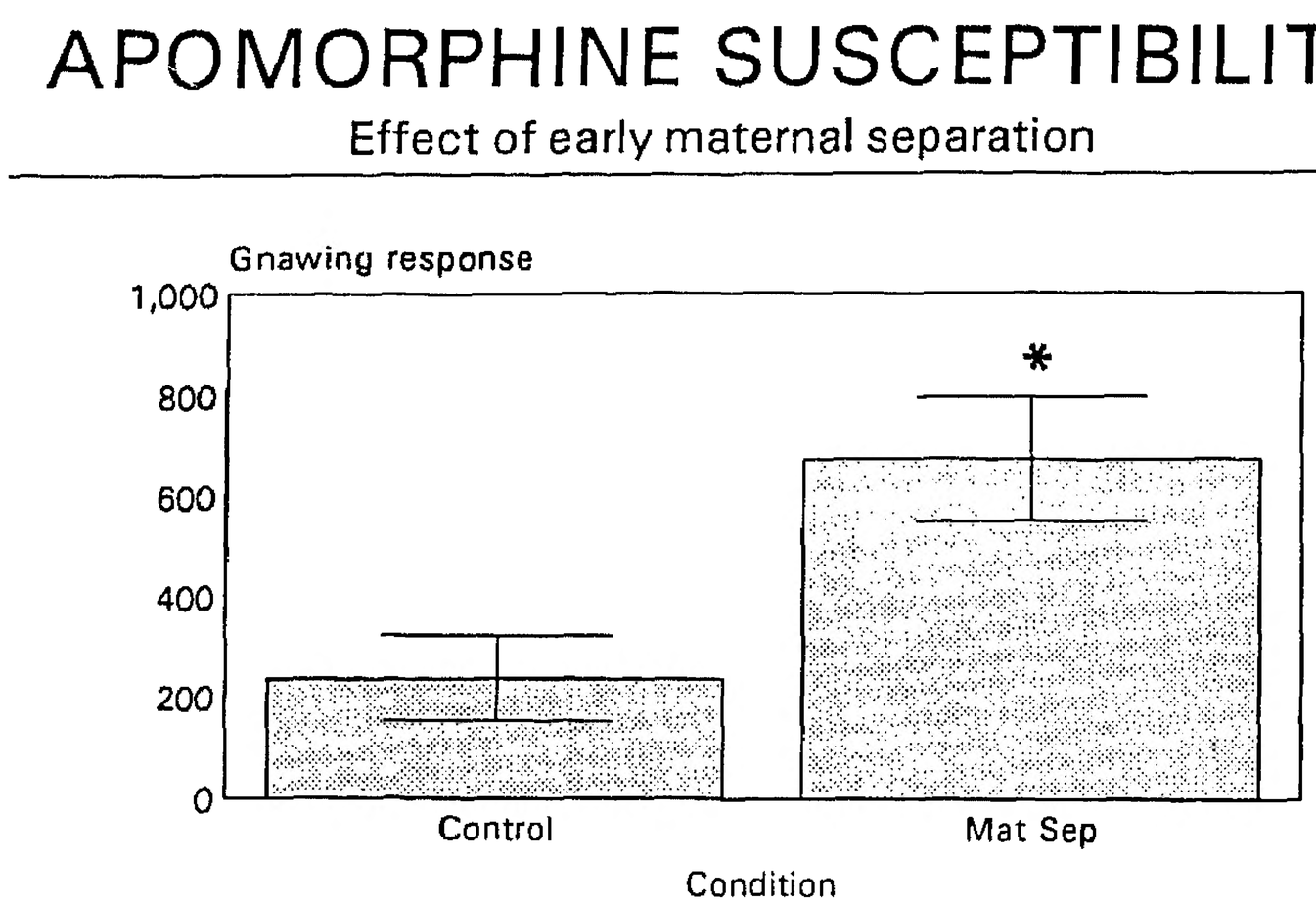

*Figure 2: The effects of early maternal separation on apomorphine susceptibility. Mat Sep : maternal separation. * $p < 0.005$ maternal separation vs control.*

The result of the apomorphine susceptibility test are displayed in figure 2. The results clearly show a significantly greater gnawing score for the maternally deprived animals as compared to the control rats. This was again confirmed by the statistical analysis ($F_{(1,30)}=9.1$, $p < 0.005$).

DISCUSSION

Rats, during the early neonatal period are totally dependent on their mother. It is therefore not surprising that changes in the early mother-infant relationship has profound influence on the subsequent development of the infant rats. The results of the present study show that rats, when deprived from their mother for 24 h at day 10 of age showed an enhanced sensitivity for

apomorphine induced gnawing at the age of 60 days. This is in close agreement with others who have found enhanced sensitivity to amphetamine (9) and reduced sensitivity to haloperidol (10) after early maternal separation.

Interestingly, these rats also showed a disruption of latent inhibition as observed in the conditioned taste aversion paradigm. Latent inhibition refers to the detrimental effect of prior stimulus preexposure on the subsequent conditioning of the stimulus. It has been argued that latent inhibition is due to the fact that animals learn to ignore the stimulus during preexposure and subsequently pay less attention to it (12). If this is true, the disruption of latent inhibition observed in the present study could be due to the fact that maternal separation disrupts this selective attention process. This is of great importance, since schizophrenic patients also show disrupted latent inhibition (15) and disrupted selective attention (16). In other words the early maternal separation may induce a condition which, in some ways resembles schizophrenia. The finding that early maternal separation leads to both enhanced sensitivity to apomorphine and disrupted latent inhibition is in agreement with earlier findings of a negative correlation between these two phenomena in normal rats (11), as well as in pharmacogenetically selected animals (Ellenbroek et al, subm).

The mother-infant interrelationship is highly complex and involves aspects of maternal care, body warmth, food giving etc. The relative importance of these individual aspects for the effects observed in the present study is still largely unclear. One important aspect seems to be body temperature. Thus rats separated at low temperatures showed decreased amounts of catecholamines, whereas rats separated at higher temperatures showed increased amounts of dopamine (16). Likewise Zimmerberg and Shartrand have found that maternally deprived animals kept at 34° C showed a reduced sensitivity to amphetamine, whereas those maternally deprived rats which were kept at 20° C showed an enhanced sensitivity to amphetamine (9). This seems to be in agreement with the present finding of enhanced apomorphine responsiveness in relatively cold (22 - 24 °C) maternally separated rats.

Irrespective of whether other factors may also play a role, it is well known that maternal separation has a profound impact on the hypothalamic-pituitary-adrenal (HPA) axis (17). Normally, very young animals have a relatively hyporesponsive stress system during the first two weeks of life (18). It has been argued that this hyposensitive period protect the central nervous system from excessive damage by corticosteroids (8,18). Early maternal separation is one way of "overriding" this hyposensitive period (17) and is likely to produce cell damage. The area most

sensitive for this is the hippocampus. This structure is known to possess large amounts of glucocorticoid and mineralocorticoid receptors (19), and to be particularly sensitive to prolonged glucocorticoid exposure (20). It is therefore likely that early postnatal stress will affect the neuronal growth particularly in the hippocampus. This is of great importance, since lesion of the hippocampus is known to disrupt latent inhibition (21,22,23). It is thus conceivable that the reduced latent inhibition observed in the present study may well be due to the disruptive effect of enhanced circulating glucocorticoid during the early postnatal period. More detailed neuropathological research is, however, necessary to confirm this. Nevertheless, it may be of great importance, given the wealth of data suggesting early neuropathological changes in the hippocampus of schizophrenic patients (24).

In summary, the present study showed that early maternal separation leads to an enhanced sensitivity of the adult rats to apomorphine and to a disruption of latent inhibition as measured with the conditioned taste aversion. It is argued that these features are likely due to a reduction in the dopaminergic system on the one hand and disturbances in the hippocampus on the other hand. Given the fact that schizophrenia is more and more regarded as a developmental disturbances, such early maternal separation may well lead to new models of schizophrenia like abnormalities. Further research into other aspects of information processing known to be disturbed in schizophrenia (like prepulse inhibition and P_{50} gating) are currently underway.

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