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ORIGINAL INVESTIGATION

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Effects of perinatal anoxia on the acute locomotor response to repeated amphetamine administration in adult rats

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Abstract We examined the possibility that anoxia at birth can alter behavioral sensitization to amphetamine during adulthood. Male rats born either vaginally or by Cesarean section with or without an additional 15-min period of anoxia received five once-daily injections of either *d*-amphetamine (2.0 mg/kg, IP) or vehicle or no pretreatment. One week later, all animals received a challenge injection of amphetamine (0.5 mg/kg, IP). The data indicate that all three birth groups of animals pretreated with amphetamine had sensitized equally to the drug's behavioral effect. Of animals pretreated with saline, however, only those born by Cesarean section with added anoxia displayed a sensitized response to amphetamine, suggesting that the stress of daily injection was sufficient to sensitize these animals to amphetamine. These findings provide experimental support for clinical evidence implicating obstetric complications, such as perinatal anoxia, in the pathophysiology of schizophrenia.

Key words Cesarean section · Locomotor activity · Birth complications · Schizophrenia · Dopamine · Behavioral sensitization

Introduction

Increasing evidence points to a link between the incidence of obstetric complications and risk of developing schizophrenic symptoms (Pollack et al. 1966; Pollin and Stabenau 1968; Woerner et al. 1973; Lewis and Murray 1987; DeLisi et al. 1988; O'Callaghan et al. 1992; Brixey et al. 1993; Norman and Malla 1993; Verdoux and Bourgeois 1993; Günther-Genta et al. 1994). One consequence common to many obstetric complications is a transient period of anoxia to the fetus. How an anoxic episode at birth would increase susceptibility to schizophrenia is open to speculation. One possibility is by altering central dopamine (DA) function. Schizophrenia, particularly the positive symptoms of the disease, is thought to reflect a functional hyperactivity of ventral tegmental DA neurons that innervate nucleus accumbens (NAcc) and other subcortical regions (Davis et al. 1991; Sunahara et al. 1993; Seeman 1995).

Experimental evidence suggesting that obstetric complications may later alter central DA function is starting to emerge. Bjelke et al. (1991) found increased tyrosine hydroxylase-immunoreactive cells in the ventral tegmental area and substantia nigra of rats that had been subjected to an anoxic episode following Cesarean birth. Perinatal asphyxia has also been reported to induce long-term changes in various neurotransmitter systems including mesencephalic DA neurons (Loidl et al. 1994) as well as short-term alterations in markers for transcription factors such as Fos (Dell'Anna et al. 1995). We have recently reported that Cesarean birth, with or without an added period of anoxia, enhances stress-induced DA release in NAcc during adulthood (Brake et al. 1997).

Dopamine has been implicated in the pathophysiology of schizophrenia in part by evidence that some of the cardinal symptoms of the disease are exacerbated by stimulants such as amphetamine (Connell 1958; Janowski and Risch 1979; Lieberman et al. 1990) and by stress (Joseph et al. 1979), both of which are known to stimulate DA release in animals (Wilcox et al. 1986; Zetterström et al. 1988; Abercrombie et al. 1989; Maisonneuve et al. 1990; Doherty and Gratton 1992; Banks and Gratton 1995). With repeated intermittent administration, animals will sensitize to the acute locomotor stimulant effect of amphetamine and other drugs that facilitate DA transmission (see review by Kalivas and Stewart 1991). In addition to its behavior arousing effects, mild stress stimulates mesocorticolimbic DA transmission and with repeated exposure animals will sensitize to both effects (Antelman 1988; Doherty and Gratton 1992). Moreover, repeatedly stressing an animal will not only sensitize it to the effects of subsequent stress but also to those of stimulants (Antelman et al. 1980; Robinson 1988; Sorg and Kalivas 1991). Thus, behavior-

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al sensitization to stimulants and stress is viewed as one of the more compelling animal models of altered DA function presumed to underlie some schizophrenic symptoms.

In the present study, we further investigated the possibility that perinatal factors can influence central DA function during adulthood. Specifically, we examined in a rat model of Cesarean birth whether an episode of anoxia alters the development of sensitization to the locomotor stimulant effects of amphetamine during adulthood. It was hypothesized that animals that had undergone Cesarean birth, with or without an additional period of anoxia, would sensitize more readily to the stimulant effects of amphetamine.

Materials and methods

Intra-uterine anoxia

All procedures were carried out in strict accordance with the guidelines established by the Canadian Council on Animal Care. Rats were delivered via Cesarean section and asphyxiated according to methods modified from those first reported by Bjelke et al. (1993). On the day of parturition, Sprague-Dawley dams (Charles River, St Constant, Québec) were decapitated and hysterectomized; this typically took 30–40 s. In one birth group, designated C+15 (Cesarean section +15 min of anoxia), the isolated intact uterus, including the fetuses, was immediately immersed in a 37°C saline bath for 13.5 min. The period of anoxia was defined as the time the uterus was immersed in the saline bath (13.5 min) to the moment the pups began breathing on their own. All the pups were then delivered from the uterus within approximately 1.5 min of removal from the bath and, if necessary, were gently palpated to initiate breathing. No other measure was necessary to resuscitate the pups which, in all but a few exceptions, readily survived the period of anoxia. Although it may appear severe, the extent of asphyxia insult resulting from this procedure is relatively moderate. In comparison to humans, the rat brain at birth is much more resistant to anoxic episodes (Jilek et al. 1970). A second birth group comprised pups born by Cesarean section with no added period of anoxia (C+0). These animals were delivered from the uterus immediately after hysterectomy. Thus, apart from the time taken to deliver the pups from the uterus, animals in the C+0 group were not subjected to any additional period of anoxia. Finally, a third group of animals comprised pups that were born vaginally (VAG).

Both groups of pups delivered by Cesarean section were placed on a heating pad until they had fully recovered. Pups of the C+0 group breathed regularly without prompting and exhibited color, muscle tone and activity levels comparable to those observed in VAG pups 1–2 min after birth. In contrast, C+15 pups breathed at a reduced rate, exhibited poor color, lacked muscle tone and remained inactive for 15–20 min after birth. Although vital signs were not monitored in the present study, Bjelke et al. (1991) reported that heart rate in similarly treated pups remained relatively stable at 140–160 beats/min during the initial 5–7 min of anoxia before decreasing steadily to 80–100 beats/min after 15 min. The same authors also found variable levels of oxygen saturation in anoxic pups; levels ranged from 10 to 35% after 15 min of anoxia.

Pups were cross-fostered with surrogate dams in litters of ten pups/dam and each litter comprised pups from each of the three birth groups; body weight in C+0 and C+15 animals were previously reported to be comparable to or greater than that of VAG animals at 1, 5, 12 and 24 h after birth (El-Khodor and Boksa 1997). A code consisting of a small amount of indelible ink injected into one of the paws was used to later identify animals from different birth groups. Only male pups were included in the study to avoid confounding group effects with sex differences. Upon weaning at 21 days, animals were randomly paired and housed on a 12-h light/dark cycle (lights on at 0800 hours) with food and water available ad libitum.

Procedure

Groups of VAG, C+0 and C+15 animals (n=36/group) were tested at 3–4 months of age. Locomotor activity was monitored between 0900 and 1400 hours in 12 activity chambers housed in a dimmed room. Each chamber (30×40×40 cm) was equipped with two photoelectric switches; light beam interruptions from each chamber were monitored and stored by a microcomputer. During the Baseline session, the spontaneous locomotor activity of all animals was monitored for 3 h. Twelve animals from each birth group were then assigned to one of three pretreatment conditions such that each group had comparable mean total spontaneous activity scores. Animals from each birth group were injected at the beginning of each of five consecutive daily 3-h sessions either with *d*-amphetamine sulfate (2.0 mg/kg, IP) or an equal volume of the saline vehicle (1 ml/kg, IP). Animals assigned to the no-pretreatment condition were simply placed in the locomotor chambers for 3 h on each of the 5 days. One week after pretreatment day 5, all animals received a challenge injection of amphetamine (0.5 mg/kg, IP) after which locomotor activity was monitored for 3 h. Each animal was tested in the same chamber throughout the experiment.

Data analysis

Statistical comparisons between birth groups (VAG, C+0 and C+15) and pretreatment conditions (amphetamine, saline, no pretreatment) were based on differences in total locomotor activity scores, defined here as the sum of photobeam interruptions recorded during a 3-h session. A one-way analysis of variance (ANOVA) was used to assess differences between birth groups on spontaneous activity scores recorded during the Baseline session. A repeated measures two-way ANOVA was used to establish, within each pretreatment condition, whether activity scores in the three birth groups differed significantly between test days. The effects of birth group and pretreatment condition on locomotor activity elicited by the amphetamine challenge injection were tested for significance with a two-way ANOVA. Differences between birth group and pretreatment condition on activity scores recorded during the first pretreatment session (day 1) were also assessed with a two-way ANOVA. This analysis was performed to uncover any birth group differences in the acute locomotor response to the pretreatment when the animals were still naive to experimental conditions. When indicated, post-hoc comparisons were performed using Tukey's Honestly Significant Difference (HSD).

Results

Baseline session

Spontaneous locomotor activity scores recorded during the Baseline session did not differ significantly between birth groups [$F(2,81)=1.879$, $P=0.1593$]; the mean total activity scores (±SEM) for the VAG, C+0 and C+15 groups of animals were 1074.42 (±75.49), 952.06 (±54.27) and 1093.20 (±75.98), respectively.

Pretreatment day 1

This analysis revealed a significant interaction of birth group and pretreatment effects on locomotor activity

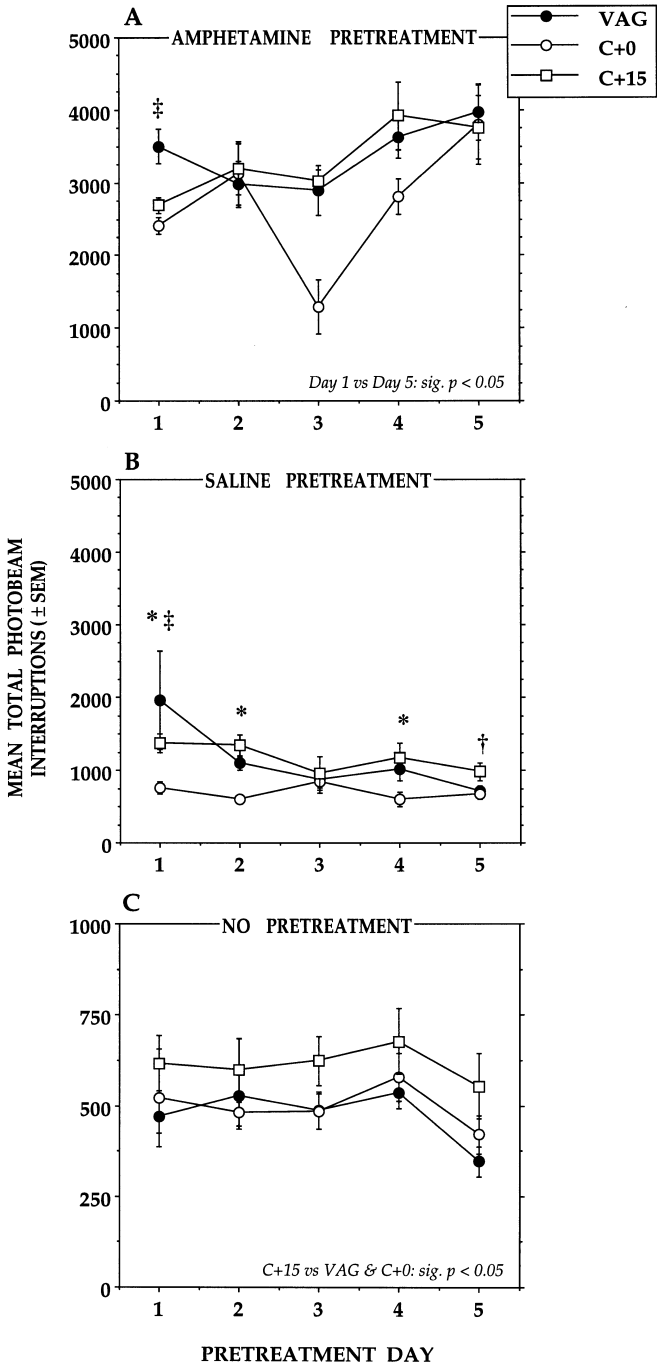

Fig. 1 **A**–**C** Mean total photobeam interruptions (±SEM) recorded during each of the five pretreatment sessions from separate birth groups of animals that received once daily *d*-amphetamine (2.0 mg/kg, IP), saline (1 ml/kg, IP) or no pretreatment. **A** Amphetamine pretreatment: overall activity scores were higher on day 5 compared to day 1 ($P<0.05$); ‡ indicates higher activity scores on day 1 in VAG group compared to C+0 ($P<0.01$) and C+15 ($P<0.05$) groups. **B** Saline pretreatment: † indicates lower activity scores in VAG group on day 5 compared to day 1 ($P<0.01$); à indicates higher activity scores on day 1 in VAG group compared to C+0 group ($P<0.01$); * indicates lower scores on days 1, 2, and 4 in C+0 group compared to C+15 and VAG groups ($P<0.05$). **C** No pretreatment: overall activity scores were higher in C+15 group compared to C+0 and VAG groups ($P<0.05$). Abbreviations: *VAG* vaginally born; *C+0* Cesarean section with no added anoxia; *C+15* Cesarean section with 15 min of added anoxia

scores of the first pretreatment session [$F(4,87)=3.575$, $P=0.0095$; Fig. 1]. Post-hoc comparisons indicated that the first amphetamine injection elicited significantly greater increases in locomotor activity scores in the VAG group of animals than in animals of the C+0 ($P<0.01$) and C+15 ($P<0.05$) groups. Furthermore, while there were no birth group differences in animals assigned to the no pretreatment condition, activity scores during the first saline pretreatment session were significantly higher in the VAG group of animals than in animals of the C+0 group ($P<0.01$).

Differences within pretreatment condition

Amphetamine

Locomotor activity scores differed significantly between test days in animals that received amphetamine as the pretreatment [$F(4,132)=3.137$, $P=0.0168$; Fig. 1A]; there was no effect, however, of birth group or of a birth group by pretreatment day interaction. Subsequent analysis confirmed that, overall, activity scores on the last amphetamine pretreatment day were significantly higher than those seen on day 1 ($P<0.05$).

Saline

There was a significant interaction of birth group and test day on activity scores when animals received once-daily saline injections as the pretreatment [$F(8,132)=2.796$, $P=0.0068$; Fig. 1B]. Post hoc analysis indicated that, whereas activity scores for the C+0 and C+15 groups of animals did not differ across pretreatment days, activity scores for the VAG group of animals on saline pretreatment day 5 were significantly lower than those on day 1 ($P<0.01$). The analysis also indicated that activity scores of animals in the C+0 group were significantly lower than those of the C+15 group on says 2 and 4 ($P<0.05$) and of both the VAG and C+15 groups on day 1 ($P<0.01$).

No pretreatment

There was a significant effect of birth group on the activity scores of animals assigned to the no pretreatment condition [$F(2,132)=5.272$, $P=0.0103$] but none of test day or of a birth group by test day interaction (Fig. 1C). Subsequent analysis confirmed that, overall, activity scores for the C+15 group of animals were higher than those of animals in the C+0 and VAG groups ($P<0.05$).

Amphetamine challenge

The amphetamine challenge injection produced increases in locomotor activity scores, the magnitude of which was

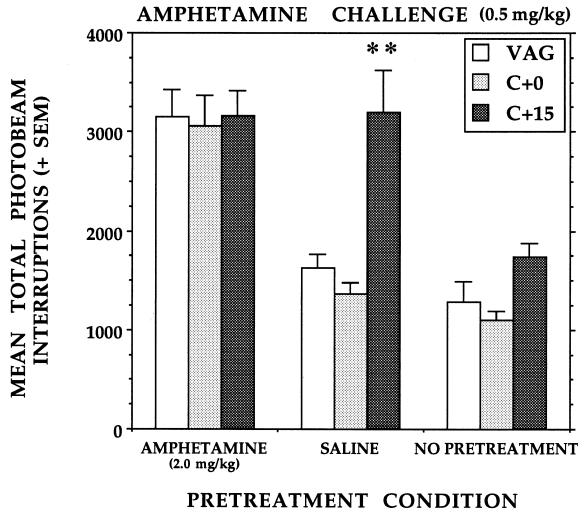

Fig. 2 Mean total photobeam interruptions (+SEM) recorded during the amphetamine challenge session in separate birth groups of animals 1 week after receiving once daily amphetamine or saline or no pretreatment. ** Indicates significantly higher activity scores in C+15 compared to C+0 and VAG groups of saline-pretreated animals ($P<0.01$)

significantly affected by birth group [$F(2,98)=10.661$, $P=0.0001$], pretreatment history [$F(2,98)=42.372$, $P<0.0001$] and by an interaction of birth and pretreatment conditions [$F(4,98)=4.065$, $P=0.0043$; Fig. 2]. Analysis of simple main effects revealed that the three birth groups of amphetamine-pretreated animals did not differ in their response to the challenge injection ($P>0.05$). This was true also of animals with no pretreatment history ($P>0.05$). There was, however, a significant effect of birth group among saline-pretreated animals [$F(2,98)=16.840$, $P=0.0001$]; post-hoc analysis confirmed that the amphetamine challenge injection produced greater increases in activity scores in animals of the C+15 group than in either of the other two birth groups of animals ($P<0.01$).

Discussion

Adult animals that sustain a period of anoxia during Cesarean birth will sensitize to the locomotor stimulant effect of amphetamine under conditions that do not lead to sensitization when animals are born vaginally or by Cesarean section without added anoxia. Thus, whereas all three birth groups of amphetamine-pretreated animals appeared to sensitize equally to the drug's locomotor stimulant effect, similar evidence of behavioral sensitization was observed only in the C+15 group of animals when saline was given as the pretreatment. The most obvious explanation for this finding is that the stress associated with each daily saline injection was sufficient to sensitize these animals to the effects of the amphetamine challenge. This conclusion is supported by the fact that none of the three birth groups of animals with no pretreatment history differed in their response to the amphetamine challenge and by a large body of evidence indicating that the behavioral effects of stress will cross-sensitize with those of stimulants (Antelman 1988; Robinson 1988).

That a mild stress should sensitize C+15 animals more readily to the effects of amphetamine is congruent with some but not all of our previously reported findings (Brake et al. 1997). In that study we found that stress-induced DA release in NAcc of adult animals that had sustained 5 (C+5) or 15 (C+15) min of anoxia following Cesarean birth became progressively more pronounced with each daily test; in contrast, no day-to-day enhancement of the acute NAcc DA stress response was found in animals born vaginally. However, contrary to the present results, animals born by Cesarean section with no added anoxia (C+0) also developed a sensitized NAcc DA response to stress. Thus, whereas birth by Cesarean section was a sufficient condition for the development of a sensitized NAcc DA response to stress, a period of added anoxia during Cesarean birth was apparently necessary for stress-induced behavioral sensitization to amphetamine. It could be argued that IP saline administration represents a milder stress than the 15-min period of tail pinch used in our previous study. If so, then it is possible that the stress associated with each saline injection was insufficient to sensitize all but those animals that had been subjected to 15 min of anoxia after Cesarean birth. Other than this, we can presently offer no explanation for this discrepancy.

A decrease in locomotion concomitant to an increase in stereotypy is an obvious but unlikely explanation for the relatively weaker locomotor response of C+0 and VAG saline-pretreated animals to the drug challenge. Stereotypic behaviors (e.g. grooming, focused sniffing) that are incompatible with locomotion and that normally occur at high doses of amphetamine can also be observed in sensitized animals in response to lower doses of the drug. However, the within-session pattern of increased locomotion elicited by the drug challenge is inconsistent with that of animals engaged in stereotypic behaviors (see Fig. 3). Had this been the case, activity counts would have been low during the first 30–60 min of the session, when brain levels of amphetamine are presumably highest, but would have been expected to increase during the latter part of the session (Segal and Kuczenski 1987). Our data indicate instead that changes in locomotor activity paralleled the rise and fall in brain concentrations of amphetamine.

While significant birth group differences in spontaneous activity were not seen during the Baseline session, the C+15 group of non-pretreated animals were generally more active than C+0 and VAG animals across pretreatment test days. Thus, the extent to which spontaneous locomotor activity was affected by birth anoxia is unclear from the present data. Differences were also seen between birth groups in the animals' locomotor response to each daily saline injection. However, these did not predict birth group differences in the locomotor response to the amphetamine challenge injection. Animals of the

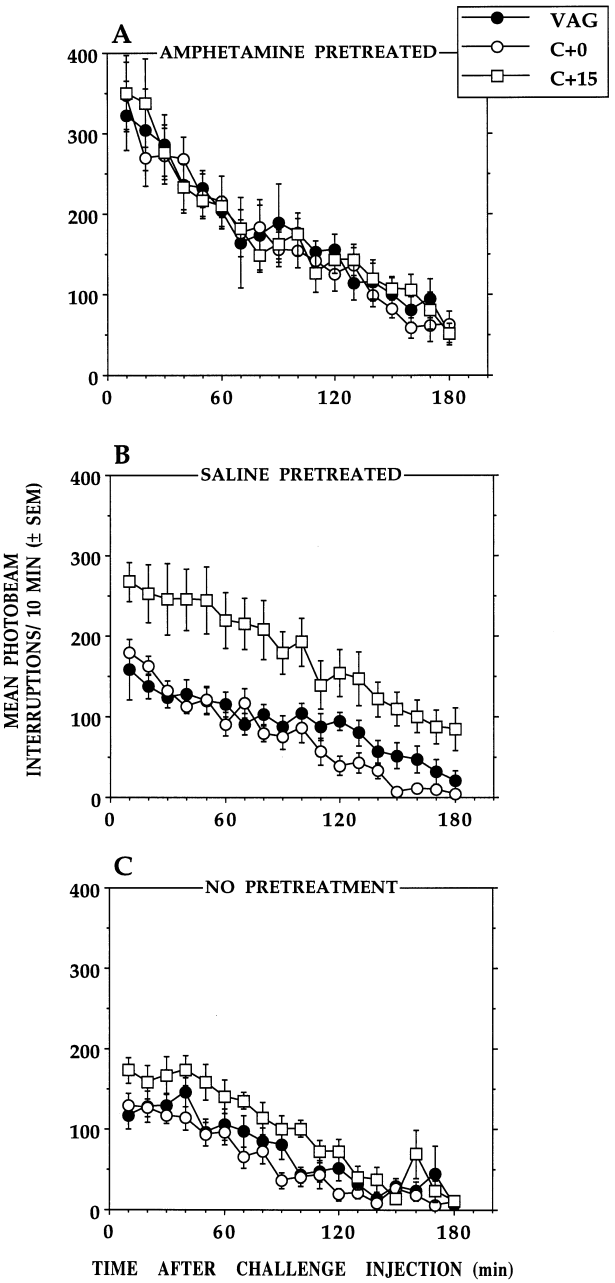

Fig. 3A–C Mean photobeam interruptions (±SEM) recorded at 10-min intervals in separate birth groups of **A** amphetamine-, **B** saline- or **C** non-pretreated animals following the amphetamine challenge injection (0.5 mg/kg, IP)

C+0 group were generally less active following each saline injection than VAG and C+15 animals which had comparable activity scores throughout the 5 pretreatment days. Yet, the amphetamine challenge data indicate that the effects of repeated saline injections on the C+15 group of animals differed from those on the two other birth groups. Similarly, the present data indicate C+0 and C+15 animals were initially subsensitive to the locomotor stimulant effect of amphetamine; when compared to the group of VAG animals, locomotor activity recorded on amphetamine pretreatment day 1 was lower for these two groups of animals. The functional significance of this finding is difficult to assess. On the one hand, the initial subsensitivity to amphetamine seen in the present study did not predict which birth group of animals would develop sensitized responses to the drug; evidence of behavioral sensitization was found in all three birth groups of amphetamine-pretreated animals and only in the C+15 group of saline-pretreated animals. Furthermore, the three birth groups of animals with no pretreatment history did not differ in their response to the challenge injection of a low dose of amphetamine; since this was also their first drug injection, C+0 and C+15 animals should have, but did not, display a similar initial subsensitivity. On the other hand, a similar subsensitivity to the acute effects of amphetamine has been reported by others. Loidl et al. (1994), for instance, found that animals that had been exposed to a minimum of 20 min anoxia at birth later displayed decreased striatal DA release in response to an acute injection of amphetamine (2.0 mg/kg) when compared to controls. Furthermore, in a study that investigated the long-term effects of premature birth, Blanchard et al. (1992) found that rats born by Cesarean section 1 day prior to parturition displayed a reduced locomotor response to acute amphetamine injection (2.0 mg/kg) when compared to vaginally born controls. Interestingly, this subsensitivity was not observed at a lower dose of amphetamine (viz. 0.5 mg/kg); this finding is consistent with the present data showing that the birth groups of non-pretreated animals responded similarly to the lower, challenge dose of amphetamine. It should be noted, however, that since animals born via Cesarean section on the day of parturition were not included in the study of Blanchard et al. (1992), it is difficult to determine if these effects can be attributed to premature birth or the Cesarean procedure. Nevertheless, taken together with the present results, these findings suggest that the influence of perinatal factors on central DA function is experience-dependent. As such, they also underscore the importance of examining the acute response to repeated amphetamine administration.

There are several factors intrinsic to the Cesarean procedure which may have contributed to results of the present study. These have been discussed in detail elsewhere (Brake et al. 1997). Briefly, in comparison to VAG animals, C+0 animals have reduced levels of plasma catecholamines at birth (El-Khodor and Boksa 1997) and of plasma corticosteroids at least 1 h after birth (Boksa 1997). Since both catecholamines and corticosteroids promote maturation of lung function during the first few hours after birth (Walters and Olver 1978; Fisher et al. 1991), a period of hypoxia to the fetus is very likely a consequence intrinsic to the Cesarean section procedure used here. Yet, adult C+0 and C+15 animals perform normally on generalized testing of sensorimotor function, although animals of the latter group do show subtle deficits in acquisition of a spatial memory task (Boska et al. 1995). More important perhaps, both C+0 and C+15 animals have a blunted corticosterone response to stress as well as reduced levels of type I glucocorticoid recep-

tors in hippocampus and hypothalamus (Boksa et al. 1996). Thus, the changes in hypothalamic-pituitary-adrenal axis function suggested by these findings may also have contributed to alter the development of stress-induced behavioral sensitization to amphetamine.

In conclusion, the findings reported here add to a body of experimental evidence indicating that long-term changes in central DA function can occur as a result of obstetric complications involving an episode of anoxia to the fetus. Specifically, the present results suggest that one consequence of these changes is an increased responsiveness of mesolimbic DA neurons to behavioral sensitizing agents such as stress and stimulants. Among other things, these findings provide experimental support for mounting clinical evidence linking the incidence of obstetric complications with the risk of developing schizophrenic symptoms.

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