Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain Research 992 (2003) 281–287
BRAIN RESEARCH
www.elsevier.com/locate/brainres

Research report

Anoxia at birth induced hyperresponsiveness to amphetamine and stress in postpubertal rats

Ismael Juárez[a], Adriana B. Silva-Gómez[a], Fernando Peralta[b], Gonzalo Flores[a,*]

[a] *Laboratorio de Neuropsiquiatría, Instituto de Fisiología, Universidad Autónoma de Puebla, 14 Sur 6301, CP 72570, Puebla, Mexico*
[b] *Centro Internacional de Psicoterapia e Investigación, 6 norte 202D, CP 72760 Cholula, Puebla, Mexico*

Accepted 28 August 2003

Abstract

Several evidences suggest that transient global anoxia after Caeraean section birth in rats produces behavioral changes related to dopaminergic transmission. However, all of the reports tested the behavioral changes in adult rats. Here we investigated the role of perinatal anoxia on behavioral paradigms related to dopamine (DA) such as novel environment, saline injection, D-amphetamine, apomorphine and stress-induced changes in locomotor activity at prepubertal and postpubertal ages. All these dimensions of behavior can be affected in schizophrenia. Caesarean section birth with or without an additional period of anoxia was performed in Sprague–Dawley rats and their behaviors were studied at P35 and P56, respectively. In addition, a third group of animals born vaginally served as control. No significant differences in saline injection and D-amphetamine-induced locomotion were observed when the three groups of rats at P35 were compared. However, stress-induced locomotor activity was significantly increased in the Caesarean birth plus anoxia at P35, while after puberty (at P56), saline injection, D-amphetamine and stress-induced locomotion were significantly enhanced in the Caesarean birth plus anoxia compared to its control groups. The data suggests that anoxia at birth mediates differently the functional development and maturation of DA behaviors in adult rats.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Anoxia at birth; Locomotion; Dopamine behavioral responsiveness and birth complications

1. Introduction

Accumulated evidence suggests that at least some cases of schizophrenia could have their origin in birth complications [18] such as a transient period of anoxia to the fetus. This obstetric complication may cause an early neurodevelopmental defect [26,27], which presumably alters the cytoarchitecture of the limbic brain areas [1,2,27,32] and produces a deregulation of the dopaminergic system [36]. Clinical features of schizophrenia typically appear in early adulthood [25] and are exacerbated by D-amphetamine [19] and stressful life events [21]. The neuroleptic drugs, DA D2-like receptors antagonist, may in part control the symptoms [31,33]. According to previous reports, adult rats that had been subjected to a transient anoxic episode at birth were sensitized more readily to the effects of repeated stress on the nucleus accumbens (Nacc) dopamine (DA) release [5], amphetamine and stress-induced locomotor activity [6,12,13]. Therefore, anoxia at birth alters the Nacc DA release in response to stress in adult rats [5]. The medial part of the prefrontal cortex (mPFC) has been implicated in the pathophysiology of schizophrenia [37] and exerts an important regulatory control on the subcortical DA system, mainly, the overactivity which is believed to underlie some of the psychotic symptoms of the disease [17,36]. We found that a neonatal lesion of the mPFC produces postpubertal behavioral changes related with DA activity [8,14]. The mPFC is interconnected with the limbic cortex directly through intracortical projections [16,20], which projects to the ventral tegmental area (VTA), the main source of mesocorticolimbic DAergic projections [29]. Furthermore, the

* Corresponding author. Tel.: +522-244-1657; fax: +522-233-4511.
E-mail address: gflores@siu.buap.mx (G. Flores).

0006-8993/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2003.08.060

mPFC efferents to the VTA controls the DA output to the nucleus accumbens (Nacc) [22,34]. Additional mPFC connections include direct glutamatergic excitatory projections to the Nacc [10,30].

Biochemical studies have indicated that anoxia at birth alters the function of the subcortical DA systems [3,4]. However, all these studies have only shown that anoxia at birth results in a DA hyperactivity in the adult rat [5,6]. While schizophrenia symptoms appear after puberty, i.e., in adolescence or early adulthood, it is important to understand the role of the anoxia at birth on the maturation of the DA system before and after puberty. In the present investigation, we have evaluated the developmental consequences of anoxia at birth. At pre- and postpubertal ages, animals were tested in behavioral paradigms commonly used to assess the functioning of the mesolimbic DA system, which demonstrated a postpubertal onset of increased novel environment and amphetamine-induced locomotion in the anoxia at birth group. While apomorphine and stress-induced locomotion were increased at both ages in the C plus anoxia group. The results suggest an important role of anoxia at birth in the functional maturation of behavior related with schizophrenia and subcortical DA activity.

2. Materials and methods

2.1. Animals

Pregnant Sprague–Dawley rats were obtained on day 20 of gestation from our animal facilities (University of Puebla). Animals were individually housed in a temperature- and humidity-controlled environment on a 12-h light–dark cycle with free access to food and water. Intrauterine anoxia was induced as described previously [5,6]. On the day of parturition (22 days of gestation), Sprague–Dawley dams were decapitated and hysterectomized. The entire uterus, including the fetus, was quickly isolated and immediately immersed in a 37 °C saline bath for 10 min (C plus anoxia). The pups were removed from the uterus and stimulated by gentle rubs to initiate breathing. The umbilical cord was ligated and the pups were placed on a heated pad until they were paired with a foster dam. Survival was 96% following 10 min of birth anoxia.

One group of controls consisted of pups that were removed from the uterus immediately after being delivered by Caesarean section (C-only). All the procedure between the hysterectomy of the dam and the removal of the fetus from the uterus was 40 s and survival was 100% in this group. After the procedure, the pups were placed under a heat pad for recovery and then they were paired with a foster dam. The other group was the one born vaginally (V-control). Pups were cross-fostered by surrogate dams and each dam was matched with an equal number of pups. Only male pups were included in the present study. A small quantity of indelible India ink was injected into one of the paws of each pup to identify the condition of the animal. On P21 the animals were weaned and grouped two or three animals per cage. All surgical procedures described in this study are in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Mexican Council for Animal Care as approved by the BUAP Animal Care Committee. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Behavioral testing

Five (P35, prepubertal rats) or 8 weeks (P56, postpubertal animals) after birth, the locomotor activity of C-only ($n=8–9$ per age group), V-control ($n=8–9$ per age group) and C plus anoxia ($n=8–9$ per age group) rats were assessed in eight-photocell activity boxes ($20\times40\times30$ cm) connected to a computer counter (Tecnologia Digital, Mexico). The locomotor activity of each animal was assessed under three testing conditions: (1) After exposure to a novel environment: unacclimatized rats were placed in an activity box for a 60 min period while the locomotor activity score was recorded. (2) After apomorphine injection: 2 days after the first test, rats were again placed in the activity boxes, and basal locomotor activity was recorded for 60 min. Animals were injected first with 1 ml/kg 0.1% ascorbid acid/0.9% NaCl solution (s.c.) and 60 min later they were injected with a 0.5 mg/ml solution of apomorphine hydrochloride (ICN Biomedicals, Aurora, OH) dissolved in 0.1% ascorbid acid/0.9% NaCl (0.5 mg/kg free base, s.c.), and the locomotor activity was subsequently recorded for 90 min. (3) After D-amphetamine injection: 48 h after the apomorphine injection, the animals were placed in the activity boxes where they were kept for a 60-min habituation period, injected first with 1 ml/kg 0.9% NaCl (s.c.) and 60 min later with a 0.5 mg/ml solution of D-amphetamine sulfate (Sigma, St. Louis, MO, USA) dissolved in 0.9% NaCl (0.5 mg/kg free base, s.c.) and the locomotor activity was recorded for the next 120 min.

Other groups of animals at P35 ($n=8$ per condition group) or P56 ($n=8$ per condition group) were assessed for repeated stress. The locomotor activity of each animal was assessed for five consecutive days for 60 min after 2 h of restricted movement. Each animal was introduced in a restricted acrylic container for 2 h and immediately they were placed in the activity boxes.

2.3. Data analysis

Behavioral results were analyzed by applying two-way ANOVA, followed by Newman–Keuls tests for post-hoc comparisons, with a conditioned birth group and age as independent factors ($p<0.05$ was considered significant). The results of the locomotor activity after restricted movement were analyzed with a repeated measure ANOVA.

3. Results

The pre- (P35) and postpubertal (P56) effects of the anoxia at birth on locomotor activity in a novel environment are illustrated in Fig. 1. At both age groups, either in control groups (C-only and V-control) or C plus anoxia, active exploratory behavior was the initial response of rats placed in a novel environment. Two-way ANOVA revealed that the locomotion was significantly affected by the anoxia

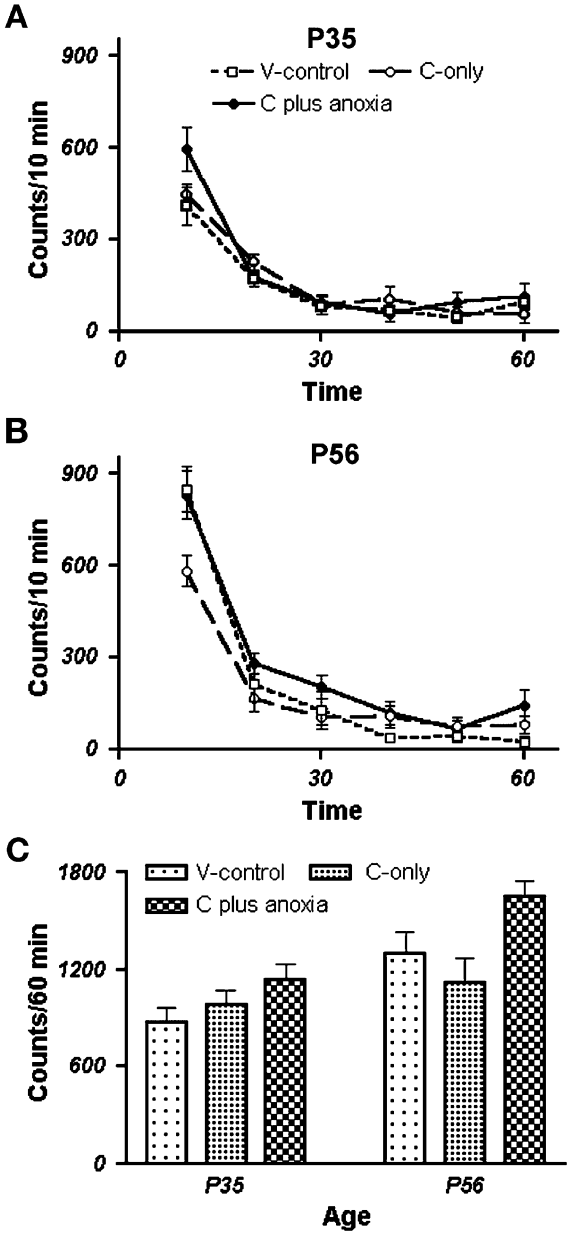

Fig. 1. Locomotor activity (mean number of beam interruptions per 60 min ± S.E.M.; $n = 8–9$ per group) in a novel environment of V-control, C-only and C plus anoxia rats at P35 and P56. Locomotor activity was determined as described in Materials and methods. (A) Temporal profile of locomotor activity at P35. (B) Temporal profile of locomotor activity at P56. (C) Analysis of total activity scores reveals that C plus anoxia rats at P56 are more active compared with their corresponding controls.

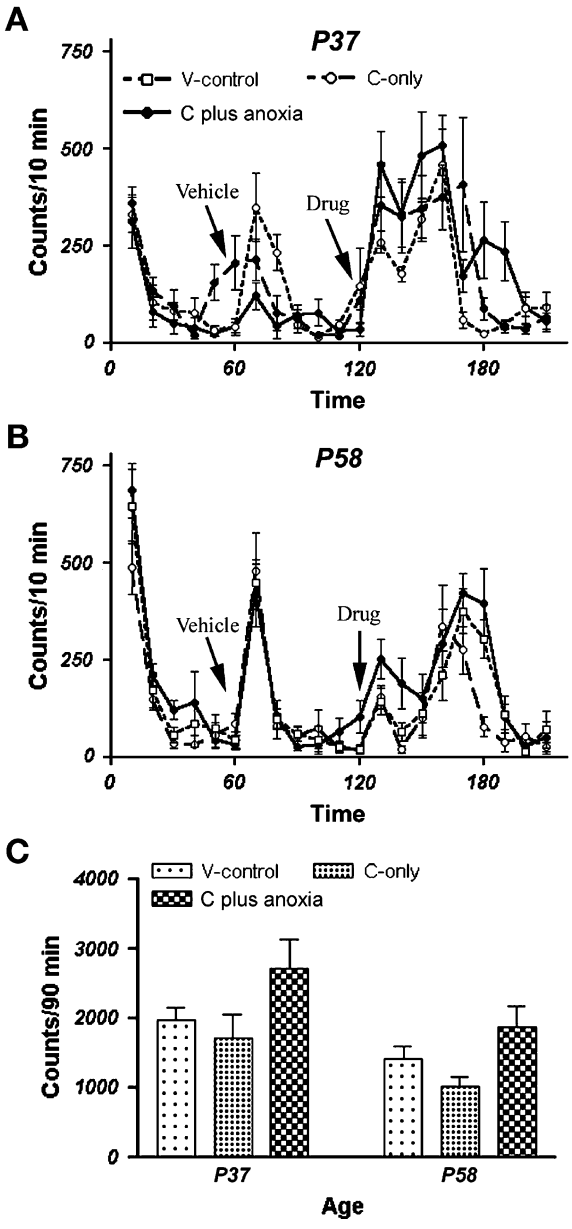

Fig. 2. Locomotor activity after vehicle and apomorphine administration (0.5 mg/kg, s.c.) of C plus anoxia or V-control and C-only (mean number of beam interruptions per 10 min ± S.E.M.; $n = 8–9$ per group). (A) Temporal profile of locomotor activity at P37. (B) Temporal profile of locomotor activity at P58. (C) Analysis of total activity scores after apomorphine reveals that C plus anoxia rats are more active compared with their controls at both ages.

($F_{2,54} = 5.52$, $p < 0.01$), by age ($F_{1,54} = 14.9$, $p < 0.001$), without differences between anoxia × age interactions ($F_{2,54} = 1.51$, $p = 0.2$). However, the C plus anoxia rats at P56 were more active than their corresponding control groups (Fig. 1A and C), while at P35, all the groups exhibited similar spontaneous locomotor activity (Fig. 1B and C).

Fig. 2 shows the effect of anoxia at birth, at pre- (P37) and postpubertal (P58) on apomorphine-induced locomotion. The analysis by a two-way ANOVA revealed the significance of anoxia ($F_{2,40} = 7.16$, $p = 0.002$) as well as

by age ($F_{1,40}=11.66$, $p=0.0015$) without differences between anoxia × age interactions ($F_{2,40}=0.14$, $p=0.8$) (Fig. 2). However, the C plus anoxia rats at both ages were more active after apomorphine administration than their corresponding control groups (Fig. 2). No significant effect of vehicle injection (two-way ANOVA, between anoxia: $F_{2,40}=0.01$ $p=0.9$; between age $F_{1,40}=1.65$ $p=0.2$; interaction anoxia × age: $F_{2,40}=2.13$ $p=0.13$) was observed in any of the groups (Fig. 3).

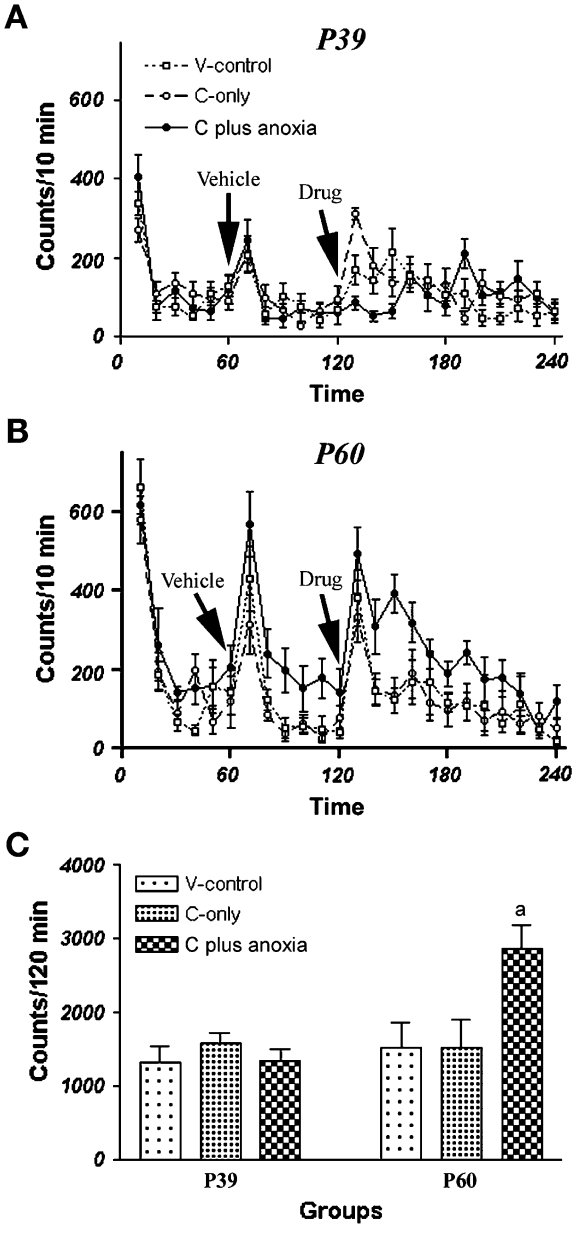

Fig. 3. Locomotor activity after vehicle (saline) and D-amphetamine administration (0.5 mg/kg, s.c.) of C plus anoxia or V-control and C-only (mean number of beam interruptions per 10 min ± S.E.M.; $n=8-9$ per group). (A) Temporal profile of locomotor activity at P39. (B) Temporal profile of locomotor activity at P60. (C) Post-hoc analysis of total activity scores after D-amphetamine reveals that C plus anoxia rats are significantly more active compared with their controls only at P60 ($^{a}p<0.01$).

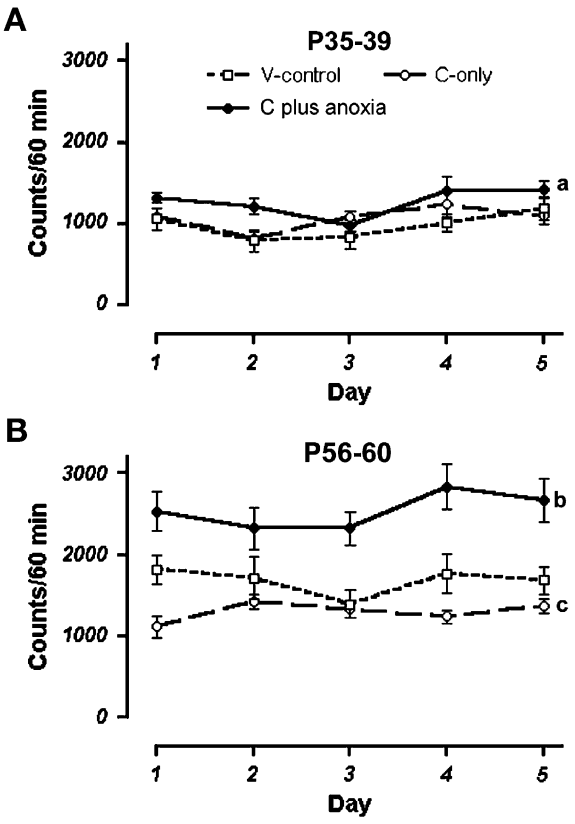

Fig. 4. Locomotor activity after 2 h of restrain stress for 5 days in the C plus anoxia or V-control and C-only (mean number of beam interruptions per 60 min ± S.E.M.; $n=8$ per group). Post-hoc analysis of locomotor activity scores for 5 days of restrain stress reveals that C plus anoxia rats are significantly more active compared with their controls at both ages (P35–39: ^{a}C plus anoxia vs. V-control or C-only $p<0.05$, P56–60: ^{b}C plus anoxia vs. V-control or C-only $p<0.001$). In addition, at P56–60: C-only rats are significantly less active compared with V-control ($^{c}p<0.05$).

Amphetamine administration induced a marked increase in the locomotion activity at P39 and P60 in anoxia after birth in rats (Fig. 3). Analysis of the entire period of D-amphetamine effects (two-way ANOVA, between anoxia: $F_{2,44}=3.46$, $p=0.040$; between age $F_{1,44}=5.88$, $p=0.019$; interaction anoxia × age: $F_{2,44}=4.5$, $p=0.016$) (Fig. 3) revealed no significant differences in the locomotor activity between V-control, C-only and C plus anoxia rats at P39. Locomotion-induced amphetamine, however, was significantly increased at P60 in C plus anoxia animals when compared with V-control and C-only ($p<0.01$) (Fig. 3C). Analysis of the saline (vehicle) injection effect (two-way ANOVA, between anoxia: $F_{2,44}=5.09$, $p=0.01$; between age $F_{1,44}=10.9$, $p=0.001$; interaction anoxia × age: $F_{2,44}=4.65$, $p=0.014$) (Fig. 3) revealed no significant differences in the locomotor activity between groups at P39, while C plus anoxia rats at P60 exhibited a hyperresponsiveness in the first minutes after vehicle application compared with their corresponding control groups ($p<0.001$) (Fig. 3).

In a new group of animals, the restriction stress test for 5 days (Fig. 4), both P35–39 and P56–60 C plus anoxia and

control animals (V-control and C-only), exhibited active locomotor behavior after 2 h of restriction. However, repeated measures one-way ANOVA ($F_{5,20} = 3.34$, $p < 0.0001$, $n = 8–10$ per group) revealed that the locomotion was significantly higher in C plus anoxia animals at both ages, compared with their corresponding controls (P35–39 C plus anoxia vs. V-control and C-only $p < 0.05$; P56–60: C plus anoxia vs. V-control and C-only $p < 0.001$). No significant difference in the locomotion was observed between V-control and C-only animals at P35–39, however, C-only exhibited a decrease in the locomotion after the restriction stress test compared with V-control at P56–60.

4. Discussion

The major aim of the present study was to evaluate the pre- and postpubertal changes in the DA-related behavior in the animal model of anoxia at birth. In addition, our results suggest the age-dependent nature of the effects of anoxia at birth on these behaviors linked to the mesolimbic DA system. We report here that this procedure induces an increase in locomotor behavior at P56, evident after saline injection as well as after D-amphetamine administration. Furthermore, as demonstrated by the evaluation at two different ages, the behavioral changes in the stress-induced locomotor activity were presented at both ages (P35 and P56), while the amphetamine effect was only exhibited at P56.

Our data in adult rats (P56) are consistent with previous reports using the same anoxia at birth paradigm [5,6,12]. In these studies, rats with anoxia at birth showed increased locomotor activity in response to either repeated stress or amphetamine administration [6,12]. In addition, the findings presented here suggest that the DA-related behavioral changes were exacerbated after puberty and support the hypothesis that some cases of schizophrenia could have their origin in birth complications [18] such as anoxia at birth. The mechanism by which anoxia at birth induces a DA-related behavior after puberty is not clear at this time. However, the apparent hyperresponsiveness of the mesolimbic DA neurons suggested by the present behavioral data and previous reports [5,11] may be explained by examining the structures that regulate the mesolimbic DA system. The limbic–cortical regions may modulate mesolimbic DA transmission, in particular, the mPFC [8,11,14]. Furthermore, the mPFC is regulated by the hippocampal formation via glutamatergic projections [16,20]; this cortical structure also sends excitatory projections to the VTA, the source of the mesolimbic DA system and the Nacc [22,29,34], both structures are interconnected [10,30]. In recent years, some evidence has accumulated which implicates the mPFC, the hippocampal formation, the Nacc and the mesolimbic DA system in anoxia at birth [3,4]. For example, anoxia at birth caused a hyperresponsiveness to amphetamine, to a novel environment, to stress, etc. Although all these studies on anoxia at birth in the adult rat provides important information about the structures that may in part be participating in behavioral changes, they do not address the consequences of anoxia at birth on the development of subcortical DAergic activity, such as our results show before and after puberty. Thus, it is possible that our finding of anoxia at birth in rats corresponds with some of the features of human schizophrenics, for example, exacerbation of the mesolimbic DA-related behavior after puberty. However, more studies are necessary in this animal model as well as the analysis of the behavioral and biochemistry changes at different ages in order to understand better the developmental process.

By comparison, the bilateral ventral hippocampal (VH) lesion in the neonatal rat (P7) has been proposed as an animal model to test the hypothesis that early neurodevelopmental abnormalities lead to behavioral changes linked to schizophrenia, because it results in the development of hypersensitivity to stress, and to direct (apomorphine) or indirect (D-amphetamine) DA agonists, which appear only after puberty [7,15,23,24]. Similar to our results in anoxia at birth, these reports in the neonatal VH lesion demonstrated that a novel environment, stress and amphetamine induced locomotor activity after puberty, while apomorphine induced locomotion before and after puberty. These similarities suggest that anoxia at birth may in part alter the VH or the connectivity between the VH with the mPFC as the principal hypothesis used to explain the DA-related behavioral changes in the neonatal VH lesion [14,36]. In addition, El-Khodor et al. [11] reported that anoxia at birth produced changes in the DA D3 receptors in the Nacc in the same sense as compared to our previous report in the neonatal VH lesioned rats [15]. In another neurodevelopmental model, the neonatal mPFC lesion results in enhanced Nacc DA release in response to repeated stress [8] and increases in amphetamine-induced locomotion with increase in D2 receptor levels in the shell of the Nacc in the adult rat [14]. Furthermore, animals with neonatal mPFC damage also show a hyperresponsive plasma corticosteroid response to restrain stress [8]. Therefore the mPFC is involved in these two neurodevelopmental animal models [8,14,23]. Furthermore, several evidences suggest that a developmental neuropathology of the frontal cortex may be involved in the aetiology of schizophrenia [35]. In particular, it has been suggested that error in the development of the mPFC may, in part, underlie this illness [36]. Several studies have demonstrated that the mPFC plays a role in behavior, Nacc DA sensitization [28] and stress response [9,10]. Therefore, Brake et al. [8] has postulated that anoxia at birth may be affecting the neurodevelopmental function of the mPFC similar to a neonatal VH lesion [7,15] or a neonatal mPFC lesion [8,14]. While our data emphasize that anoxia at birth may be related with some of the features of human schizophrenia in these two neurodevelopmental animal models (neonatal VH lesion and neonatal mPFC lesion), such as a postpubertal increase in mesolimbic DA-related behavior.

In conclusion, anoxia at birth leads to an augmented age-related factor in the DA-related behavior. The mechanism related to this augmented age-related behavior after puberty is still unknown, while the behavioral consequences of the anoxia at birth in the adult rat were characterized as described previously [5,6,12,13]. However, the anoxia at birth resulted in induced locomotion after the saline injection and D-amphetamine, which appeared after puberty (P56), while the stress-induced hyperlocomotion was detected before puberty.

Acknowledgements

This study was supported by grants from SEP-VIEP-BUAP (No. IV-19102) and CONACyT-Mexico (No. 40664-Q). We are grateful to Dr. Carlos Escamilla for his help and suggestions in the management of the animals. IJ is a master degree student from BUAP with studentship from CONACyT. GF is a member of the National System of Researchers from Mexico.

References

[1] S. Akbarian, W.E. Bunney Jr., S.G. Potkin, S.B. Wigal, J.O. Hagman, C.A Sandman, E.G. Jones, Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in the frontal lobe of schizophrenics implies disturbances of cortical development, Arch. Gen. Psychiatry 50 (1993) 169–177.

[2] S.E. Arnold, V.M.Y. Lee, E.R. Gur, J.Q. Trojanowski, Abnormal expression of two microtubule associated proteins (MAP2 and MAP5) in specific fields of the hippocampal formation in schizophrenia, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 10850–10854.

[3] B. Bjelke, K. Andersson, S.O. Ögren, P. Bolme, Asphyctic lesion: proliferation of tyrosine hydroxylase-immunoreactive nerve cell bodies in the rat substantia nigra and functional changes in dopamine neurotransmission, Brain Res. 543 (1991) 1–9.

[4] P. Boksa, A. Krishnamurthy, W. Brooks, Effects of a period asphyxia during birth on spatial learning in the rat, Pediatr. Res. 37 (1995) 489–496.

[5] W.G. Brake, M.B. Noel, P. Boksa, A. Gratton, Influence of perinatal factors on the nucleus accumbens dopamine response to repeated stress during adulthood: an electrochemical study in the rat, Neuroscience 77 (1997) 1067–1076.

[6] W.G. Brake, P. Boksa, A. Gratton, Anoxia at birth enhances sensitization to the locomotor stimulant effect of amphetamine in the adult rat, Psychopharmacology 133 (1997) 389–395.

[7] W.G. Brake, R.M. Sullivan, G. Flores, L.K. Srivastava, A. Gratton, Neonatal ventral hippocampal lesions attenuate the nucleus accumbens dopamine response to stress: an electrochemical study in the adult rat, Brain Res. 831 (1999) 25–32.

[8] W.G. Brake, G. Flores, D. Francis, M.J. Meaney, L.K. Srivastava, A. Gratton, Enhanced nucleus accumbens dopamine and plasma corticosterone stress responses in adult rats with neonatal excitotoxic lesions to the medial prefrontal cortex, Neuroscience 96 (2000) 687–695.

[9] A.Y. Deutch, The regulation of subcortical dopamine systems by the prefrontal cortex: interactions of central dopamine systems and the pathogenesis of schizophrenia, J. Neural Transm. 36 (1992) 61–89.

[10] M.D. Doherty, A. Gatton, Medial prefrontal cortical D1 receptor modulation of the meso-accumbens dopamine response to stress: an electrochemical study in freely behaving rats, Brain Res. 715 (1996) 86–97.

[11] B.F. El-Khodor, P. Boksa, Long-term reciprocal changes in dopamine levels in prefrontal cortex versus nucleus accumbens in rats born by caesarean section compared to vaginal birth, Exp. Neurol. 145 (1997) 118–129.

[12] B.F. El-Khodor, P. Boksa, Birth insult increases amphetamine-induced behavioral responses in the adult rat, Neuroscience 87 (1998) 893–904.

[13] B.F. El-Khodor, P. Boksa, Transient birth hypoxia increases behavioral response to repeated stress in the adult rat, Behav. Brain Res. 107 (2000) 171–175.

[14] G. Flores, G.K. Wood, J.J. Liang, R. Quirion, L.K. Srivastava, Enhanced amphetamine sensitivity and increased expression of dopamine D2 receptors in postpubertal rats after neonatal excitotoxic lesions of the medial prefrontal cortex, J. Neurosci. 16 (1996) 7366–7375.

[15] G. Flores, D. Barbeau, R. Quirion, L.K. Srivastava, Decreased binding of dopamine D3 receptors in limbic subregions after neonatal bilateral lesion of rat hippocampus, J. Neurosci. 16 (1996) 2020–2026.

[16] P.S. Goldman-Rakic, L.D. Selemon, M.L. Schwartz, Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the Rhesus monkey, Neuroscience 12 (1984) 719–743.

[17] M. Goldstein, A.Y. Deutch, Dopaminergic mechanisms in the pathogenesis of schizophrenia, FASEB J. 6 (1992) 2413–2421.

[18] F. Gunther-Genta, P. Bovet, P. Hohlfeld, Obstetric complications and schizophrenia. A case-control study, Br. J. Psychiatry 164 (1994) 165–170.

[19] D.S. Janowski, M.K. El-Youset, J.M. Davis, H.J. Sekerke, Provocation of schizophrenic symptoms by intravenous administration of methylphenidate, Arch. Gen. Psychiatry 28 (1973) 185–191.

[20] T.M. Jay, M.P. Witter, Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaseolus vulgaris*-leucoagglutinin, J. Comp. Neurol. 313 (1991) 574–586.

[21] M.H. Joseph, C.D. Frith, J.L. Waddington, Dopaminergic mechanism and cognitive deficits in schizophrenia: a neurobiological model, Psychopharmacology 63 (1979) 273–280.

[22] M. Karreman, B. Moghaddam, The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area, J. Neurochem. 66 (1996) 589–598.

[23] B.K. Lipska, D.R. Weinberger, Delayed effects of neonatal hippocampal damage on haloperidol-induced catalepsy and apomorphine-induced stereotypic behaviors in the rat, Dev. Brain Res. 75 (1993) 213–222.

[24] B.K. Lipska, G.E. Jaskiw, D.R. Weinberger, Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia, Neuropsychopharmacology 9 (1993) 67–75.

[25] J. Marengo, Classifying the courses of schizophrenia, Schizophr. Bull. 20 (1994) 519–536.

[26] T.F. McNeil, E. Cantor-Graae, Minor physical anomalies and obstetric complications in schizophrenia, Aust. N. Z. J. Psychiatry 34 (2000) S65–S73.

[27] T.F. McNeil, E. Cantor-Graae, D.R. Weinberger, Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophrenia, Am. J. Psychiatr. 157 (2000) 203–212.

[28] G. Mittleman, P.A. LeDuc, I.Q. Whishaw, The role of D1 and D2 receptors in the heightened locomotion induced by direct and indirect dopamine agonists in rats with hippocampal damage: an animal analogue of schizophrenia, Behav. Brain Res. 55 (1993) 253–267.

[29] S.R. Sesack, V.M. Pickel, Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area, J. Comp. Neurol. 320 (1992) 145–160.

[30] S.R. Sesack, A.Y. Deutch, R.H. Roth, B.S. Bunney, The topograph-

ical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with *Phasseolus vulgaris* leucoagglutinin, J. Comp. Neurol. 290 (1989) 213–242.

[31] J.C. Schwartz, D. Lévesque, M.P. Martres, P. Sokoloff, Dopamine D_3 receptor: basic and clinical aspects, Clin. Neuropharmacol. 16 (1993) 295–314.

[32] R.L. Suddath, G. Christison, E.F. Torrey, M.F. Casanova, D.R. Weinberger, Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia, N. Engl. J. Med. 322 (1990) 789–794.

[33] R.K. Sunahara, P. Seemann, H.H.M. Van Tol, H.B. Niznik, Dopamine receptors and antipsychotic drug response, Br. J. Psychiatry, Suppl. (1993) 31–38.

[34] M.T. Taber, H.C. Fibiger, Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: modulation by metabotropic glutamate receptors, J. Neurosci. 15 (1995) 3896–3904.

[35] D.R. Weinberger, On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia, Neuropsychopharmacology 14 (1996) 1S–11S.

[36] D.R. Weinberger, B.K. Lipska, Cortical maldevelopment, anti-psychotic drugs, and schizophrenia: a search for common ground, Schizophr. Res. 16 (1995) 87–110.

[37] D.R. Weinberger, M.S. Aloia, T.E. Goldberg, K.F. Berman, The frontal lobes and schizophrenia, J. Neuropsychiatr. Clin. Neurosci. 6 (1994) 419–427.