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RESEARCH ARTICLE

Acute perinatal asphyxia impairs non-spatial memory and alters motor coordination in adult male rats

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Abstract A large body of clinical evidence suggests a possible association between perinatal asphyxia and the onset of early, as well as long-term, neurological and psychiatric disorders including cognitive deficits. The present study investigated cognitive and motor function modifications in a well characterized and clinically relevant experimental rat model of human perinatal asphyxia. The results reported here show that adult rats exposed to a single (20 min) asphyctic episode at delivery displayed: (a) a deficit in non-spatial memory, assessed in a novel object recognition task; (b) an impaired motor coordination, measured by the rotarod test. On the other hand, gross motor activity and spatial memory, evaluated in both the Y maze and the Barnes maze, were not affected by perinatal asphyxia. The results of this study provide further insights into the long-term effects of perinatal asphyxia on neurobehavioural functions.

Keywords Asphyctic insult · Cognitive deficit · Object recognition · Rotarod · Rat

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Introduction

Perinatal asphyxia is a major birth complication occurring in approximately 1–6 per 1,000 of newborn babies and resulting in either death or various brain injuries in the affected individuals (Vannucci 2000; du Plessis and Volpe 2002; de Haan et al. 2006) being, in addition, suggested as a factor facilitating the onset of delayed psychiatric disorders (Toft 1999; McNeil et al. 2000).

A valuable and clinically relevant model for investigating human perinatal asphyxia in rodents has been developed by Bjelke and co-workers (Bjelke et al. 1991; Andersson et al. 1992; Herrera-Marschitz et al. 1993). Previous studies have demonstrated various neurological abnormalities in rats undergoing the Bjelke model of asphyxia. Thus, an altered expression of tyrosine hydroxylase (Chen et al. 1995), dopamine receptors (Chen et al. 1997b; Gross et al. 2005) as well as modifications in dopamine release (Herrera-Marschitz et al. 1994; Chen et al. 1997b), have been detected in basal ganglia and limbic regions of developing asphyxiated rats. Moreover, acute perinatal asphyxia was associated to neuronal death in the CA1 region and dentate gyrus of the hippocampus (Bjelke et al. 1991; Dell'Anna et al. 1997; Morales et al. 2005), as well as to the demise of striatal GABAergic neurons (Van De Berg et al. 2003). Notably, asphyxia-induced neuronal abnormalities have been demonstrated to persist in adult rats (Loidl et al. 1994; Herrera-Marschitz et al. 1994; Chen et al. 1997a; Kohlhauser et al. 1999), being possibly related to the delayed onset of behavioural disorders reported by clinical observations (Mañeru et al. 2003; de Haan et al. 2006).

Previous studies have investigated the manifestation of behavioural disturbances in rats subjected to acute perinatal asphyxia, mainly addressing motor function, emotional behaviour and spatial memory (Boksa et al. 1995; Hoeger et al. 2000; Loidl et al. 2000; Van De Berg et al. 2003;

Venerosi et al. 2006). No study, however, has yet investigated whether an acute perinatal asphyctic insult may have long-term effects on rat non-spatial episodic memory. On these bases, the present study evaluated the performance of adult asphyctic rats in the object recognition task, a rodent model used to assess non-spatial working memory deficits and thought to mimic the recognition tests used to evaluate amnesic syndromes in humans (Ennaceur and Delacour 1988; Reed and Squire 1997; Dix and Aggleton 1999). Moreover, in order to verify whether possible non-spatial memory deficits were associated to motor and spatial memory impairments, perinatal asphyctic rats were evaluated for gross motor activity, motor coordination and cognitive performance in both the Y maze and the Barnes maze.

Thus, in the present study rat cognitive performance was investigated by behavioural tests devoid of any stressful cues or primary reinforcers, such as swimming, food deprivation or electric shocks, largely evaluating the behaviour of the rats under ethological-like conditions (McLay et al. 1998; Morrow et al. 2002).

Materials and methods

Subjects

Three-month old male Wistar rats were used throughout the study. Rats were obtained from pregnant dams (bred at local colony) which, on gestational day 22, were anesthetized, sacrificed by neck dislocation and hysterectomized. One or two pups for each dam were promptly removed from the uterus to be used as non-asphyxiated cesarean-delivered controls. The uterine horns containing the remaining fetuses were subsequently placed in a 37°C thermostat-controlled water bath for 20 min to induce perinatal asphyxia. Following this procedure asphyctic pups were removed from uterine horns, stimulated to initiate breathing and observed for 60 min. Successively, both cesarean-delivered controls and asphyctic pups were assigned to surrogate dams for nursing. After weaning, rats were housed (5–6 per group) in Plexiglas cages under an artificial 12 h light-dark cycle (lights on at 8:00 am). Food and water were available ad libitum and standard conditions of temperature and humidity were maintained.

All experiments were conducted by an experimenter blind of rats treatment in accordance with the guidelines for care and use of experimental animals of the European Communities Directive (86/609/EEC; D.L., 27.01.1992, number 116).

Novel object recognition task

Measurement of novel object recognition is widely used for evaluating non-spatial working memory in rodents (Ennaceur and Delacour 1988). Object recognition experiments were performed in a black wooden box (length 60 cm, width 40 cm, height 30 cm) with the floor covered in sawdust. Objects to be discriminated were made of plastic or glass, differing as to shape and colour. Objects had no genuine significance and had not been previously associated to rewarding or aversive stimuli. Two days before the test, rats were allowed to explore the box twice for 5 min, in order to acclimatize. On the testing day each rat was placed in the box for two 4 min sessions and left to explore objects freely. During the first session (S1) two copies of the same object were present, whereas in the second session (S2) rats were exposed to a copy of the objects presented previously in S1 plus a novel object. S1 and S2 were separated by a 15 or 60 min interval. Exploration was defined as the rats sniffing, gnawing or touching the object with the nose, whereas sitting and/or turning around the object were not considered as exploratory behaviours. To avoid the presence of olfactory cues, objects were thoroughly cleaned after each session. Moreover, the combination of objects (novel vs. old) and their respective position (right vs. left) were counterbalanced to prevent biased preferences for particular objects or positions. The performance of the rats was videotaped and the following parameters were evaluated: (a) time spent by the rats in exploring the objects during either S1 or S2, and (b) novel object recognition. The latter was calculated as the percentage of time spent in exploring the new object, respect to the total amount of time spent in exploring the two objects during S2.

Spontaneous alternation in the Y maze

Evaluation of spontaneous alternation behaviour in a Y maze is commonly employed to investigate short-term spatial memory in rodents (Maurice et al. 1994; Yamada et al. 1996). The apparatus was made of black PVC, consisting in three equal arms (length 50 cm, width 20 cm, height 35 cm), named A, B and C. Arms converged onto a central triangular area and the floor of the maze was covered in sawdust, which was changed in between rat tests. Rats were placed in the central area and left free to explore the whole apparatus for a single 8 min trial during which their performance was videotaped. Percentage of spontaneous alternation was calculated on the basis of the sequence of arm entries as reported by Yamada et al. (1996).

Barnes maze performance

Barnes maze is widely used to evaluate long-term spatial memory in rodents (Barnes 1979; McLay et al. 1998; Komater et al. 2005). Apparatus consisted of a white acrylic (diameter 120 cm) circular platform placed 90 cm above floor level, having 18 holes (diameter 9 cm) equally

spaced around its perimeter. Experiments were performed by placing each rat individually in a square box (side 15 cm), located in the center of the apparatus, for 30 s, then the box was removed and the rat was left free to explore the whole apparatus for 4 min. During the trial the rat had to retrieve a black escape box, connected to one of the holes, by using spatial cues surrounding the maze. Both acquisition (two trials a day, for 5 days) and retention (two trials, 7 days after the end of acquisition phase) of spatial memory were investigated by measuring both latency in retrieving the escape hole (in seconds) and number of errors (an error was considered as the rat placing its nose in a hole not connected to the escape box), performed by rats. The above values were measured for each session and averaged on a daily basis.

Motor activity

Evaluation of gross motor activity was performed in Plexiglas cages (length 47 cm, height 19 cm, width 27 cm) having a metal grid over the floor and equipped with infrared photocell emitters-detectors situated along the long axis (Opto-Varimex Mini; Columbus Instruments, Columbus Ohio, USA). A counter recorded two different kinds of motor activity: (a) locomotor activity, consisting in movement of the rat along the axes of the cage, and (b) total motor activity, due to locomotion plus non-finalized movements (such as grooming, rearing and sniffing). Motor activity was evaluated 30 min a day for five consecutive days.

Rotarod performance

The rotarod test was used to evaluate motor balance and coordination (Hamm et al. 1994; Rogers et al. 1997) and consisted of (a) an acclimation session, (b) a training session and (c) a test session. During the first week, animals were acclimatized to the rotarod equipment having a rod diameter of 6.1 cm (LE 8500, Panlab s.l., Barcelona, Spain) for three consecutive days. During this session, the rats were moved to the rotarod room and placed on the immobile rotarod (at 0 rpm) for 5 min on three separate occasions, with an interval of 30 min between each trial. The rat was placed perpendicular to the rod axis with its head in the opposite direction to rotation. At the end of the acclimation period no increased defecation rate and/or refusal to exercise was displayed by animals. During the second week, animals were trained to run on the rotarod for three consecutive days. The training session was performed at a constant speed of five rotations per min (5 rpm) for 5 min twice a day; training sessions were separated by an interval of 30 min. Rats were required to move forward in order to remain on the rotating rod to avoid falling. Trained animals invariably stepped onto the rod voluntarily and did not appear particularly stressed by the rod movement. The actual rod test was performed immediately following the end of the last training session, consisting of three trials (5 min each) on the rod set at a constant speed of 5 rpm. The three trials were separated by a 30 min rest period. Trials ended once the rat had fallen and the time spent on the rod was automatically registered. Individual test rod performance was added to calculate mean time spent on the rod during the three trials.

Statistical analysis

Values are reported as means ± S.E.M. Data from object recognition task, spontaneous alternation and rotarod test were analysed by one-way ANOVA. Data from gross motor activity test and Barnes maze were analysed with two-way ANOVA for repeated measures. Significance was set at $P < 0.05$.

Results

Effects of perinatal asphyxia on memory tasks

Perinatal asphyxia impaired novel object recognition in adult rats. Asphyctic rats spent significantly less time exploring the novel object respect to controls ($F = 4.31$, $P = 0.04$), when a 60 min interval elapsed between S1 and S2 (Fig. 1c). In contrast, when a shorter (15 min) interval was used, no differences between the experimental groups were observed (Fig. 1a). There were not differences between asphyctic and control rats, when the total time spent exploring the objects was considered, either during the S1 or the S2 sessions (Fig. 1b, d).

On the other hand, perinatal asphyxia affected neither Y maze nor Barnes maze performance of rats (Table 1).

Effects of perinatal asphyxia on motor function

Rotarod performance was significantly affected by perinatal asphyxia when measured at the adult stage. Asphyctic rats showed a significant reduction in the time spent on the rotarod during the three (5 min) trial sets performed at a constant speed (5 rpm), compared to that observed in control rats ($F = 10.17$, $P = 0.003$) (Fig. 2). No significant differences, but only a tendency to a decrease, were observed in any of the test sessions. Similarly, no differences were observed during the acquisition of the task.

Furthermore, as reported by previous studies, perinatal asphyxia influenced neither the intensity of non-finalized movements, nor the time-course of the motor activity measured at adulthood (data not shown).

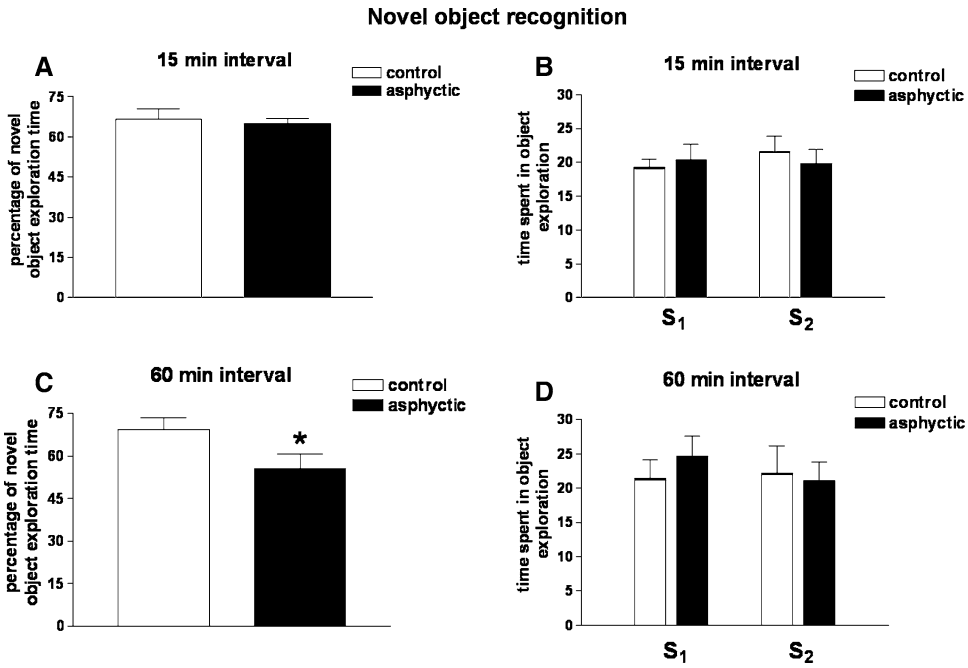

Fig. 1 Effect of acute perinatal asphyxia on novel object recognition. Asphyctic rats spent significantly less time in exploring the novel object as compared to non asphyxiated controls when a 60 min (**c**), but not a 15 min (**a**), interval between the two experimental sessions of object recognition was used. The novel object was totally unfamiliar to the rats and it was presented in combination with a familiar object that rats had experienced before. Asphyctic and control rats spent a comparable amount of time in exploring the objects presented during either *S1* or *S2* sessions for all object recognition experiments (**b**, **d**). $^{*}P < 0.05$ as compared to control rats ($n = 13$–18)

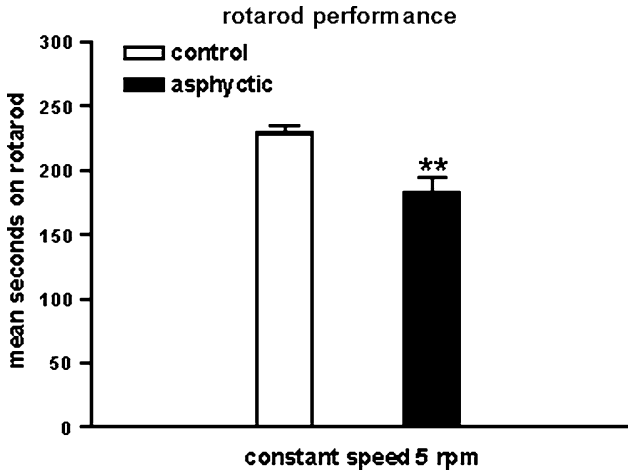

Fig. 2 Effect of perinatal asphyxia on rotarod performance at a constant speed (5 rpm) for 5 min. Mean ± S.E.M. of time spent on the rotarod across three trials by asphyctic (*black column*) and control (*white column*) rats. $^{**}P < 0.005$ asphyctic versus control rats ($n = 16$–22)

Discussion

The present study demonstrates that rats receiving a single asphyctic insult at delivery show a deficit in both non-spatial working memory and motor coordination similarly to what has been observed in humans (Mañeru et al. 2003; de Haan et al. 2006).

Cognitive functions in asphyctic rats

In the present study, adult rats subjected to an acute asphyctic insult at delivery displayed an impaired performance in the object recognition task, suggesting the presence of a deleterious effect of perinatal asphyxia on non-spatial working memory.

The novel object recognition paradigm is merely based on the rat spontaneous exploratory behaviour measured under ethological-like conditions, being devoid of the spatial reference memory component, not involving primary reinforcers or stressful cues, such as food deprivation and/or electric shocks (Ennaceur and Delacour 1988; Morrow et al. 2002). Therefore this experimental model allows to selectively investigate the presence of possible deficits in non-spatial memory, avoiding the possible interference of motivated and/or stress-mediated behaviour on memory performance, which could be the main target of the changes induced by asphyxia, as suggested for other stress-mediated behaviour (Venerosi et al. 2004; Caputa et al. 2005). It is important to point out that the asphyctic rats did not display any deficit in general motor activity during the experimental trials, and they spent a similar time exploring the objects during the S1 and/or S2 trials to that shown by the control rats. These observations suggest that the impairment in object recognition observed here is not an epiphenomenon due to either a decrease in spontaneous exploratory activity, or a reduced interest of the rats towards the objects produced by perinatal asphyxia. Interestingly, perinatal asphyxia did not seem to alter the ability of the rats for discriminating between different objects, since the asphyxia-exposed rats were capable of recognizing the novel object when a shorter (15 min) delay between the two experimental sessions for the object recognition task was used. On these bases, the impairment in novel object recognition is likely to reflect an actual specific deficit in non-spatial working memory of rats subjected to an acute episode of perinatal asphyxia.

Table 1 Effect of perinatal asphyxia on spatial memory tests

Barnes maze: latency in retrieving the escape hole (in seconds)						
	A1	A2	A3	A4	A5	C
Control	36.2 ± 5.9	25.2 ± 3.4	22.6 ± 4.3	12.2 ± 1.9	7.3 ± 1.7	15 ± 3.3
Asphyctic	35.6 ± 10.2	18.1 ± 3.6	18.4 ± 2.9	11.2 ± 1.8	8.6 ± 1.5	23 ± 10.5
Barnes maze: errors made in retrieving the escape hole						
	A1	A2	A3	A4	A5	C
Control	3.8 ± 0.8	2.9 ± 0.5	2.9 ± 0.6	1.7 ± 0.4	1.4 ± 0.3	1.9 ± 0.5
Asphyctic	3.7 ± 0.8	2.2 ± 0.4	3.0 ± 0.6	1.5 ± 0.5	1.0 ± 0.4	2.1 ± 0.6
Y maze: spontaneous alternation (% of spontaneous alternation)						
Control	73.19 ± 6.78					
Asphyctic	77.20 ± 3.87					

No differences in Barnes and Y maze performance were observed between asphyctic and control rats. *Barnes maze* mean values ± S.E.M of latency (in seconds) and errors in retrieving the escape hole are reported for each experiment day and for each group. *A* indicates a day of memory acquisition phase, *C* indicates the day of the memory consolidation test. *Y maze* no differences in the percentage of spontaneous alternation were observed between asphyctic and control rats ($n = 9–11$)

Differently from what observed in the object recognition task, the asphyctic rats used in this study did not display impairments in both Y maze and Barnes maze performance, therefore accounting for an intact spatial memory in these animals, in agreement with data from previous studies (Boksa et al. 1995; Loidl et al. 2000; Hoeger et al. 2006). Again, it is interesting to evidence that tests used in this study, differently from other paradigms previously employed to evaluate spatial memory in asphyctic rodents, did not involve reinforcers or stressors, therefore providing a measure of memory performance devoid of influences by either stress or motivation. Taken together the outcomes obtained in the analysis of rats memory performance suggest the existence of a more pronounced sensitivity of non-spatial memory to the deleterious effects of perinatal asphyctic insults.

It has been postulated how in the rat brain two distinct, although interconnected, neuronal circuits process either non-spatial or spatial memory. Non-spatial memory is processed through a pathway involving cortical associative areas, the medial thalamus and other subcortical structures; while spatial memory depends on a circuit connecting the hippocampus, prelimbic cortex and anteromedial/posterior parietal cortex (Steckler et al. 1998). Since both circuits appear affected by perinatal asphyxia (Bjelke et al. 1991; Kohlhauser et al. 1999) the lack of influence of this insult on spatial memory might be due to a differential sensitivity to asphyxia-induced neuronal damage between the two memory pathways, or to the occurrence of more robust compensatory mechanisms in the neuronal circuit processing spatial memory.

Motor functions in asphyctic rats

In line with previous results, the present study revealed no influence of perinatal asphyxia on gross motor activity. Nevertheless, asphyctic rats displayed an impairment in rotarod performance, which accounts for deficits in motor coordination and balance (Hamm et al. 1994; Rogers et al. 1997).

The deleterious neuronal modifications induced in basal ganglia by perinatal asphyxia (Kohlhauser et al. 1999; Van De Berg et al. 2003; Gross et al. 2005) may underlie the impairment of rotarod performance observed in the present study. In particular, alterations in dopaminergic transmission, markedly influenced by perinatal asphyctic insults (Herrera-Marschitz et al. 1994; Gross et al. 2005; Bustamante et al. 2006), may be critically implicated, in view of the acknowledged regulation of motor functions by dopamine (Hauber 1998; Jay 2003).

Evidences obtained in rats subjected to basal ganglia dopamine depletion demonstrated how the expression of gross motor activity is affected only by massive deficits in dopamine transmission, whereas abnormalities in motor coordination, as well as in skilled movements, emerge even in the presence of partial and/or mild reductions in dopaminergic tone (Kirik et al. 1998; Barneoud et al. 2000; Deumens et al. 2002). In a recent microdialysis study (Bustamante et al. 2006), it was shown that a decrease of dopamine release after perinatal asphyxia was only observed when the animals were challenged with a pulse of D-amphetamine, or K^+-depolarization induced by a pulse of KCl, indicating that under basal conditions

compensatory mechanisms take place, enough to help the animals to cope with standard environmental challenges. Moreover, Ogura et al. (2005) showed that rats with a partial striatal dopaminergic denervation displayed a behavioural impairment at the rotarod, but not at a condition for evaluating gross motor behaviour. In agreement, it has been shown that perinatal asphyxia is associated with subtle rather that gross alterations in basal ganglia neurocircuitries (Kohlhauser et al. 1999; Van De Berg et al. 2003; Gross et al. 2005; Klawitter et al. 2007). Those subtle changes can be reflected in tests for fine coordination movements, but not for gross or stress mediated behaviours. It should be considered, however, that brain regions other than the basal ganglia can be involved in the long-term behavioural changes produced by perinatal asphyxia, including the cerebellum, a region playing a critical role in motor coordination and balance (Thach 1998), reported to be damaged after perinatal asphyxia (Dell'Anna et al. 1997; Kohlhauser et al. 1999, 2000; Bernet et al. 2003).

Implications for human perinatal asphyxia

Clinical studies have reported the presence of both verbal and visual memory deficits and, in some cases, impaired spatial orientation, clumsiness and mild motor incoordination in children and adolescents who suffered perinatal asphyctic injury (Gadian et al. 2000; Mañeru et al. 2001a, b; Marlow et al. 2005; de Haan et al. 2006). On these bases, the results of this study appear relevant for the preclinical investigation of delayed impairments in cognitive and motor-related function following non-disabling episodes of perinatal asphyxia. The relevance of the present results is corroborated by analogies existing between the features of brain damage previously observed in the experimental model used here and those reported in humans suffering from perinatal asphyxia. Indeed, in both cases overall damages have been described as being subtle and restricted to specific regions rather than extended throughout the whole brain (Kohlhauser et al. 1999; Gadian et al. 2000; Mañeru et al. 2001a). Moreover, working memory deficits are observed in both schizophrenia and attention deficit hyperactivity disorder (Elvevag and Goldberg 2000; Schweitzer et al. 2006), and a possible relationship between perinatal asphyxia and these disorders has been suggested (McNeil et al. 2000; Boog 2004). The cognitive impairment observed might therefore enhance proper elucidation of the potential influence of perinatal asphyxia on the onset of psychiatric disturbances in later life.

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References

Andersson K, Bjelke B, Bolme P, Ögren S-O (1992) Asphyxia-induced lesion of the rat hippocampus (CA1, CA3) and the nigrostriatal dopamine system. In: Gross J (ed) Hypoxia and ischemia, CNS, vol 41. Wissenchafliche Publ. der Humboldt-Universität zu Berlin, R. Medizin, Berlin, pp 71–76

Barnes CA (1979) Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. J Comp Physiol Psychol 93:74–104

Barneoud P, Descombris E, Aubin N, Abrous DN (2000) Evaluation of simple and complex sensorimotor behaviours in rats with a partial lesion of the dopaminergic nigrostriatal system. Eur J Neurosci 12:322–336

Bernert G, Hoeger H, Mosgoeller W, Stolzlechner D, Lubec B (2003) Neurodegeneration, neuronal loss, and neurotransmitter changes in the adult guinea pig with perinatal asphyxia. Pediatr Res 54:523–528

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

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

Boog G (2004) Obstetrical complications and subsequent schizophrenia in adolescent and young adult offsprings: is there a relationship? Eur J Obstet Gynecol Reprod Biol 114:130–136

Bustamante D, Morales P, Torres Pereyra J, Goiny M, Herrera-Marschitz M (2006) Nicotinamide prevents the effect of perinatal asphyxia on dopamine release evaluated with in vivo microdialysis three months after birth. Exp Brain Res 177:358–369

Caputa M, Rogalska J, Wentowska K, Nowakowska A (2005) Perinatal asphyxia, hyperthermia and hyperferremia as factors inducing behavioural disturbances in adulthood: a rat model. Behav Brain Res 63:246–256

Chen Y, Ögren SO, Bjelke B, Bolme P, Eneroth P, Gross J, Loidl F, Herrera-Marschitz M, Andersson K. (1995) Nicotine treatment counteracts perinatal asphyxia-induced changes in the mesostriatal/limbic dopamine systems and in motor behaviour in the four-week-old male rat. Neuroscience 68:531–538

Chen Y, Engidawork E, Loidl F, Dell'Anna E, Lubec G, Andersson K, Herrera-Marschitz M (1997a) Short- and long-term effects of perinatal asphyxia on monoamine, amino acid and glycolysis product levels measured in the basal ganglia of the rat. Dev Brain Res 1004:19–30

Chen Y, Hillefors-Berglund M, Herrera-Marschitz M, Bjelke B, Gross J, Andersson K, von Euler G (1997b) Perinatal asphyxia induces long-term changes in dopamine D1, D2, and D3 receptor binding in the rat brain. Exp Neurol 146:74–80

de Haan M, Wyatt JS, Roth S, Vargha-Khadem F, Gadian D, Mishkin M (2006) Brain and cognitive-behavioural development after asphyxia at term birth. Dev Sci 9:350–358

Dell'Anna E, Chen Y, Engidawork E, Andersson K, Lubec G, Luthman J, Herrera-Marschitz M (1997) Delayed neuronal death following perinatal asphyxia in rat. Exp Brain Res 115:105–115

Deumens R, Blokland A, Prickaerts J (2002) Modeling Parkinson's disease in rats: an evaluation of 6-OHDA lesions of the nigrostriatal pathway. Exp Neurol 175:303–317

Dix SL, Aggleton JP (1999) Extending the spontaneous preference test of recognition: evidence of object-location and object-context recognition. Behav Brain Res 99:191–200

du Plessis AJ, Volpe JJ (2002) Perinatal brain injury in the preterm and term newborn. Curr Opin Neurol 15:151–157

Elvevag B, Goldberg TE (2000) Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol 14:1–21

Ennaceur A, Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats. 1: behavioral data. Behav Brain Res 31:47–59

Gadian DG, Aicardi J, Watkins KE, Porter DA, Mishkin M, Vargha-Khadem F (2000) Developmental amnesia associated with early hypoxic-ischaemic injury. Brain 123:499–507

Gross J, Andersson K, Chen Y, Muller I, Andreeva N, Herrera-Marschitz M (2005) Effect of perinatal asphyxia on tyrosine hydroxylase and D2 and D1 dopamine receptor mRNA levels expressed during early postnatal development in rat brain. Mol Brain Res 134:275–281

Hamm RJ, Pike BR, O'Dell DM, Lyeth BG, Jenkins LW (1994) The rotarod test: an evaluation of its effectiveness in assessing motor deficits following traumatic brain injury. J Neurotrauma 11:187–196

Hauber W (1998) Involvement of basal ganglia transmitter systems in movement initiation. Prog Neurobiol 56:507–540

Herrera-Marschitz M, Loidl F, Andersson K, Ungerstedt U (1993) Prevention of mortality induced by perinatal asphyxia: hypothermia or glutamate antagonism? Amino Acids 5:413–419

Herrera-Marschitz M, Luthman J, Ferré S (1994) Unilateral neonatal intracerebroventricular 6-hydroxydopamine administration in rats: II. Effects on extracellular monoamine, acetylcholine and adenosine levels monitored with in vivo microdialysis. Psychopharmacology 116:451–456

Hoeger H, Engelmann M, Bernert G, Seidl R, Bubna-Littitz H, Mosgoeller W, Lubec B, Lubec G (2000) Long term neurological and behavioral effects of graded perinatal asphyxia in the rat. Life Sci 66:947–962

Hoeger H, Engidawork E, Stolzlechner D, Bubna-Littitz H, Lubec B (2006) Long-term effect of moderate and profound hypothermia on morphology, neurological, cognitive and behavioural functions in a rat model of perinatal asphyxia. Amino Acids 31:385–396

Jay TM (2003) Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. Prog Neurobiol 69:375–390

Kirik D, Rosenblad C, Bjorklund A (1998) Characterization of behavioral and neurodegenerative changes following partial lesions of the nigrostriatal dopamine system induced by intrastriatal 6-hydroxydopamine in the rat. Exp Neurol 152:259–277

Klawitter V, Morales P, Bustamante D, Gomez-Urquijo S, Hokfelt T, Herrera-Marschitz M (2007) Plasticity of basal ganglia neurocircuitries following perinatal asphyxia: effect of nicotinamide. Exp Brain Res 180:139–152

Kohlhauser C, Mosgoeller W, Hoeger H, Lubec G, Lubec B (1999) Cholinergic, monoaminergic and glutamatergic changes following perinatal asphyxia in the rat. Cell Mol Life Sci 55:1491–1501

Kohlhauser C, Mosgoller W, Hoger H, Lubec B (2000) Myelination deficits in brain of rats following perinatal asphyxia. Life Sci 67:2355–2368

Komater VA, Buckley MJ, Browman KE, Pan JB, Hancock AA, Decker MW, Fox GB (2005) Effects of histamine H3 receptor antagonists in two models of spatial learning. Behav Brain Res 159:295–300

Loidl CF, Herrera-Marschitz M, Andersson K, You ZB, Goiny M, O'Connor WT, Silveira R, Rawal R, Bjelke B, Chen Y, Ungerstedt U (1994) Long-term effects of perinatal asphyxia on basal ganglia neurotransmitter systems studied with microdialysis in rat. Neurosci Lett 175:9–12

Loidl CF, Gavilanes AW, Van Dijk EH, Vreuls W, Blokland A, Vles JS, Steinbusch HW, Blanco CE (2000) Effects of hypothermia and gender on survival and behavior after perinatal asphyxia in rats. Physiol Behav 68:263–269

Mañeru C, Junque C, Bargallo N, Olondo M, Botet F, Tallada M, Guardia J, Mercader JM (2001a) (1)H-MR spectroscopy is sensitive to subtle effects of perinatal asphyxia. Neurology 57:1115–1118

Mañeru C, Junque C, Botet F, Tallada M, Guardia J (2001b) Neuropsychological long-term sequelae of perinatal asphyxia. Brain Inj 15:1029–1039

Mañeru C, Serra-Grabulosa JM, Junque C, Salgado-Pineda P, Bargallo N, Olondo M, Botet-Mussons F, Tallada M, Mercader JM (2003) Residual hippocampal atrophy in asphyxiated terms neonates. J Neuroimaging 13:68–74

Marlow N, Rose AS, Rands CE, Draper ES (2005) Neuropsychological and educational problems at school age associated with neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed 90:F380–F387

Maurice T, Hiramatsu M, Itoh J, Kameyama T, Hasegawa T, Nabeshima T (1994) Behavioral evidence for a modulating role of sigma ligands in memory processes. I. Attenuation of dizocilpine (MK-801)-induced amnesia. Brain Res 647:44–56

McLay RN, Freeman SM, Zadina JE (1998) Chronic corticosterone impairs memory performance in the Barnes maze. Physiol Behav 63:933–937

McNeil TF, Cantor-Graae E, Ismail B (2000) Obstetric complications and congenital malformation in schizophrenia. Brain Res Rev 31:166–178

Morales P, Reyes P, Klawitter V, Huaiquin P, Bustamante D, Fiedler J, Herrera-Marschitz M (2005) Effects of perinatal asphyxia on cell proliferation and neuronal phenotype evaluated with organotypic hippocampal cultures. Neuroscience 135:421–431

Morrow BA, Elsworth JD, Roth RH (2002) Prenatal cocaine exposure disrupts non-spatial, short-term memory in adolescent and adult male rats. Behav Brain Res 129:217–223

Ogura T, Ogata M, Akita H, Jitsuki S, Akiba L, Noda K, Hoka S, Saji M (2005) Impaired acquisition of skilled behavior in rotarod task by moderate depletion of striatal dopamine in a pre-symptomatic stage model of Parkinson's disease. Neurosci Res 51:299–308

Reed JM, Squire LR (1997) Impaired recognition memory in patients with lesions limited to the hippocampal formation. Behav Neurosci 111:667–675

Rogers DC, Campbell CA, Stretton JL, Mackay KB (1997) Correlation between motor impairment and infarct volume after permanent and transient middle cerebral artery occlusion in the rat. Stroke 28:2060–2065

Schweitzer JB, Hanford RB, Medoff DR (2006) Working memory deficits in adults with ADHD: is there evidence for subtype differences? Behav Brain Funct 2:43

Steckler T, Drinkenburg WH, Sahgal A, Aggleton JP (1998) Recognition memory in rats–II. Neuroanatomical substrates. Prog Neurobiol 54:313–332

Thach WT (1998) A role for the cerebellum in learning movement coordination. Neurobiol Learn Mem 70:177–188

Toft PB (1999) Prenatal and perinatal striatal injury: a hypothetical cause of attention-deficit-hyperactivity disorder? Pediatr Neurol 21:602–610

Van de Berg WD, Kwaijtaal M, de Louw AJ, Lissone NP, Schmitz C, Faull RL, Blokland A, Blanco CE, Steinbusch HW (2003) Impact of perinatal asphyxia on the GABAergic and locomotor system. Neuroscience 117:83–96

Vannucci RC (2000) Hypoxic-ischemic encephalopathy. Am J Perinatol 17:113–120

Venerosi A, Valanzano A, Cirulli F, Alleva E, Calamandrei G (2004) Acute global anoxia during C-section birth affects dopamine-mediated behavioural responses and reactivity to stress. Behav Brain Res 154:155–164

Venerosi A, Cutuli D, Chiarotti F, Calamandrei G (2006) C-section birth per se or followed by acute global asphyxia altered emotional behaviour in neonate and adult rats. Behav Brain Res 168:56–63

Yamada K, Noda Y, Hasegawa T, Komori Y, Nikai T, Sugihara H, Nabeshima T (1996) The role of nitric oxide in dizocilpine-induced impairment of spontaneous alternation behavior in mice. J Pharmacol Exp Ther 276:460–466