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Long Term Neurodevelopmental and Behavioral Effects of Perinatal Life Events in Rats

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Modern neurosciences are now able to open new avenues concerning an experimental approach to clinical neurosciences and psychiatry. Detection and prediction of potential vulnerabilities such as behavioral disturbances and neurodegenerative diseases, are urgent tasks leading to prevention that must be encouraged in parallel to the enormous efforts displayed for treatments. Besides possible genetic origins of diseases, environmental factors are now coming under scrutiny, and especially deleterious and challenging life events and stress occurring during prenatal and postnatal critical periods may orient brain functions towards deleterious developments. The hypothesis that will be examined is that early events might be at the origin of pathological transformations and symptoms after long periods of apparent normal abilities and behavioral homeostasis. We used models of prenatal stress and postnatal manipulations such as cross-fostering. It will be demonstrated that such events induce long-term changes, cognitive and emotional modifications appearing first, when offspring are adults, followed by cognitive defects later in life. Increased sensitivity of the hypothalamic pituitary-adrenal axis (HPA), the endocrine system controlling the secretion of stress hormones (corticoids), appears to be a major element of pathogenesis. HPA axis dysfunction appears very early after birth (3 days) and lasts for months. Cumulative exposure to high levels of hormones seems to be detrimental for some brain regions, especially the hippocampus and major neurotransmitters systems such as dopamine neurons. We evidenced that neuronal modifications in hippocampal region are correlated with behavioral and cognitive defects, relating environment, stress in early life, hormonal changes, long-term neuropathological processes and impaired cognition in aging. Moreover appears in offspring, when adults, a proneness to engage in drug dependence. These data emphasize the need to consider early environmental life events as etiological factors for delayed neuropsychiatric disturbances, neurodegenerative defects included. Moreover, they strengthen the interest for a longitudinal approach to promote experimental psychopathology.

I. INTRODUCTION: DEVELOPMENTAL PSYCHOPATHOLOGY AS AN EMERGING FIELD OF RESEARCH

By tradition the province of child psychologists and child psychiatrists, developmental psychopathology, is becoming a key discipline of its own. It emphasizes gene-environment interactions during fetal and perinatal brain development, and more generally, the possible defects arising in brain morphogenesis and connectivi-

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ties and all the neuroadaptative processes that change the normal course of brain maturation (West and King, 1987). While enormous efforts are directed to the understanding of the genetic disabilities, few is still known concerning the pathological effects of perinatal environments, prenatal in particular. Within this complex and multidimensional landscape, genes and environment often conspire to derail normal developmental pathways; prenatal and perinatal events influence individual's vulnerability and susceptibility to a range of pathological conditions. Advances in the developmental neurosciences allow now to move to identify specific genetic but also epigenetic risk factors and to develop animal models (Lekman, 1999)

Most of the data on the effects of prenatal stress in humans come from retrospective studies on children whose mothers experienced various forms of life events during pregnancy. These stress include familial and marital discord, death of the husband, proximity of an airport and the unpredictable aircraft noises associated, threat of war, etc.... These stimuli, different in nature, induced consistent changes in children's behavior and development (Huttunen and Niskanen, 1978; Schell, 1981; Stott, 1973). Indeed, children displayed long-term behavioral abnormalities such as unsociable and inconsiderate behaviors, hyperactivity-attentional deficit disorder, sleep disturbances and some psychiatric disorders including schizophrenic episodes, depressive and neurotic symptoms or drug abuse, mood and anxiety disorders (Hammen *et al* 1992; Huttunen and Niskanen, 1978; Jones and Tauscher, 1978; Meijer, 1985; Schatzberg and Nemeroff, 1995; Stott, 1973).

Recent studies have looked at links between various types of antenatal maternal psychological distress and obstetric outcome. Most of these studies, although not all (Perkin *et al.*, 1993), have pointed in the same direction: mother's stress or anxiety are linked with prematurity or low birth weight (Pagel *et al.*, 1990; Hedegaard *et al.*, 1993; Copper *et al.*, 1996), as well as a lower

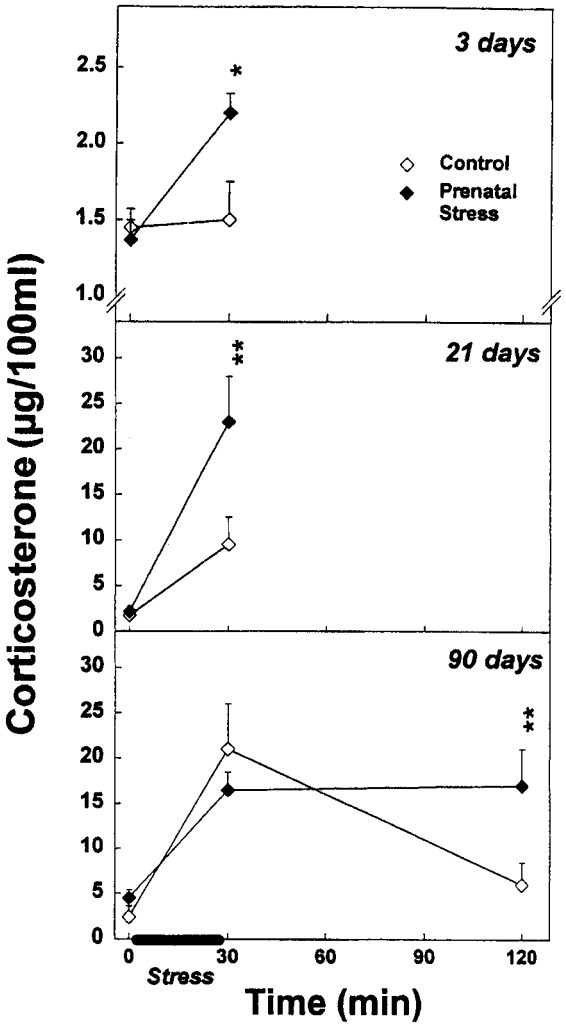

FIGURE 1 Study of corticosterone secretion after exposure to novelty in 3-, 21- and 90-day old rats. Basal levels (T0) of corticosterone were no affected by prenatal stress in 3-, 21- and 90-day old male rats. Conversely, 3 and 21 day-old offsprings of stressed mothers exhibited a significant rise in corticosterone after exposure to stress (T30), whereas control 3 day-old pups remained unresponsive. At 90 days of age the prenatally stressed animals showed no difference 30 min after stress (T30) however, after 120 min (T 120), corticosterone levels remained elevated in prenatally-stressed rats with respect to controls. Eight to 5 animals were used for each group. $^{*}p<0.05$; $^{**}p<0.01$; ◊ Control; ♦ Prenatal stress

blood circulation in the fetal middle cerebral artery that can affect fetal brain development (Sjostrom *et al.*, 1997). Prenatal stress also significantly worsened the scores on the neonatal neu-

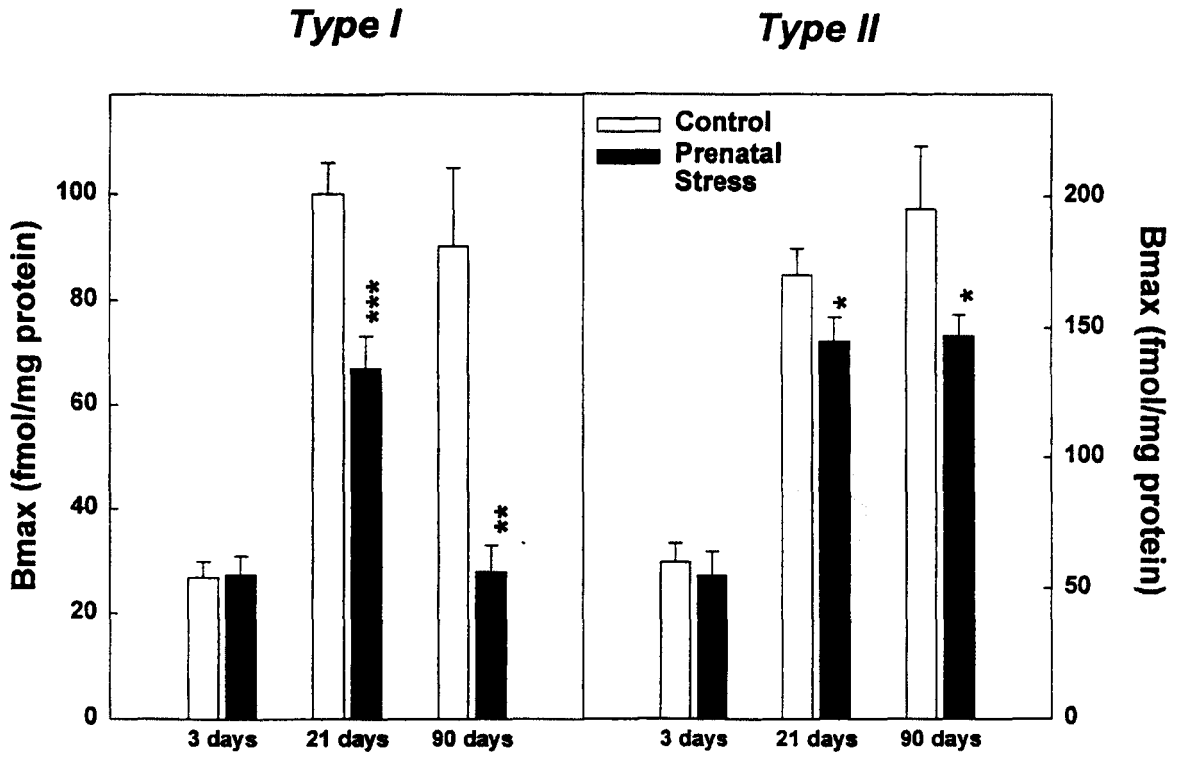

FIGURE 2 Hippocampal type I and type II corticosteroid receptor numbers in 3-, 21- and 90-day-old male rats. The maximal binding capacity (B_{max}) of type I receptors is indicated in the top of the figure. The B_{max} of type II receptors is indicated in the bottom of the figure. Type I and type II corticosterone receptor numbers were no different at 3 days of age, but were significantly lower in prenatally-stressed animals compared to controls at 21 and 90 days. At 21 days, type I was –31% and type II –18%. At 90 days of age type I was –70% and type II –30%. For the study at 3 and 21 days of age the number of animals was 1416 for group; for the study at 90 days of age 7 rats for group were used. $^{*}p<0.05$; $^{**}P<0.01$; $^{***}p<0.001$; □ Control; ■ Prenatal stress

rological examination (Lou *et al.*, 1994) and has been associated to childhood sleep problems (Armstrong *et al.*, 1998) and subsequent increased hypothalamic pituitary-adrenal(HPA) responsiveness reminiscent of major depression in adults (Barden *et al.*, 1995). It is now admitted that maternal stress in pregnancy has long-term neurodevelopmental effects on the infant, and that these may include an increased predisposition to later depression (Glover, 1997).

These behavioral disturbances and psychopathology reflect neuroadaptive processes that have occurred in consequence of such life events. Neuroadaptive processes refer to the structural and functional changes resulting from environmental constraints, such that they induce lapses of homeostatic processes. These contraints are generally repeated or chronic and imposed to the organism which cannot cope with the situation. The nervous system adapts itself and undergoes a change which is frequently long lasting if not definitive. In other words the long term effects of the physiologic response to stress refer to mechanisms now labeled as allostatic load. Allostasis is the ability of the organism to achieve stability through change (see Koob and Le Moal, 1997) and is critical to adaptation and to survival. Through allostasis the regulatory systems, and primarily the nervous system, protect the organism by responding to challenges. The price of these transactions and accommodation to environmental constraints, can be allosta-

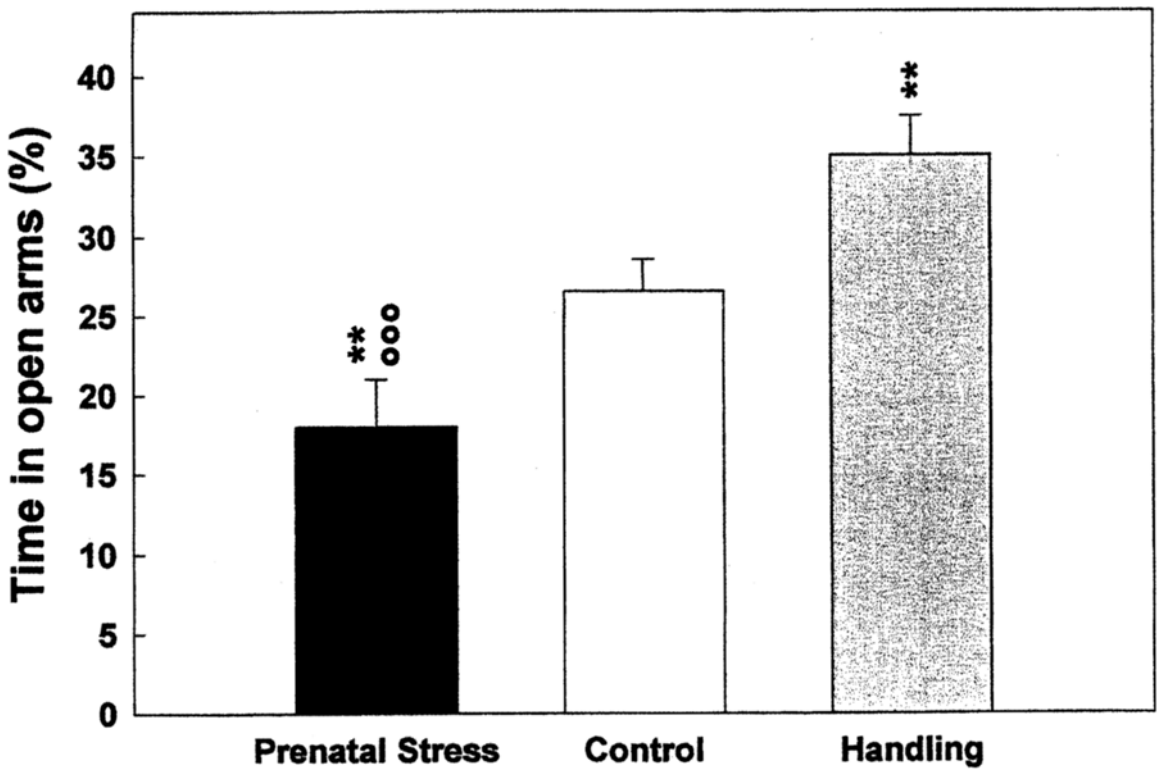

FIGURE 3 Percentage of time spent in open arms (open / open + closed) measured in the elevated plus-maze over the 10 min test (mean ± SEM). Prenatally stressed rats (n=27) had a lower score than that of control (n=61) and handled rats (n=28), whereas the score of the handled rats was higher than the one of control rats, indicating that prenatally stressed rats took refuge more than the other groups. PS versus C, $^{**}p<0.01$; PS versus H, $^{°°°}p<0.001$; H versus C, $^{**}p<0.01$)

tis load, "which is the wear and tear that results from chronic overactivity or underactivity of allostatis systems" (see McEwen, 1998). Many methods are used in adult animals to provoke these basic changes that place the brain in another state: kindling, long-term potentiation, sensitization, stress, etc... However new methodologies are now available to approach in animals, long term effects of perinatal stress.

II. PERINATAL STRESS METHODOLOGIES IN ANIMALS

Offspring stimulations in rats derives of methods inaugurated by Joffe (1965, 1969) and Ward (Ward 1972, 1984; Ward and Weisz, 1984) for prenatal stress and determination of critical periods of hormonal systems development in fetuses and by Levine (Levine, 1962, Levine and Lewis 1959, Levine *et al*, 1967) for post-natal stimulations sometimes called handling.

For the experiments that shall be described, pregnant female Wistar rats weighing between 250 g and 300 g were used. Animals were purchased from Iffa Credo (France) and shipped at the third day of pregnancy. The animals were individually housed with ad libitum access to food and water in a constant dark-light cycle (light on 06.00 h, off 18.00 h). The animal house was maintained at a temperature of 22°C and humidity was controlled (60%). Animals were

generally divided in 2 groups of 10. One group was submitted to restraint stress by placing them for 45 min in a plastic transparent cylinder (6 cm diameter, 20 cm long) three times per day (09.00, 12.00 and 17.00 hr) between the 14th and the 21stdays of pregnancy. The sessions were performed in a lighted environment. The animals of the control group were handled with the same schedule. After birth, the litters were reduced to 8 animals including all the males, who were raised by their biological mother until the 21st day of postnatal life. During the third month of postnatal life, two male rats were selected at random form each litter to form 2 groups, one containing animals from stressed mothers (prenatal stress group), and the second from control mothers (control group). This stress procedure was chosen as it has an indirect influence on the fetus via a direct stress on the mother. We evidenced that mother's corticosterone, crossing the placenta barrier, was the primary agent acting directly onto fœtus brain and organism (for review Maccari *et al.*, 1998).

An adoption procedure was used as a postnatal challenge. In our hands this method was the most accurate to stimulate pups by their mother. At birth, half of the pups were raised by their biological mother and the other half were assigned to either control of prenatally stressed foster mothers. The pups were placed in the cage of the adoptive mother within the first 3–6 hr after birth. During this procedure, the mothers were briefly (less than 1 min) removed from their cages. The offspring were weaned 21 days after birth, and left undisturbed until testing at 90 days of age. No more than three male siblings per litter were tested in adult life. To study interactions between adoption and prenatal stress necessitated complex experimental design (Maccari *et al.*, 1995). In addition to the two groups as defined above, a third and a fourth groups contained either control or prenatally stressed rats that were raised by an adoptive foster mother of the same group. Thus, the third group contained prenatally unstressed offspring adopted by a control unstressed mother, and the fourth group contained prenatally stressed offspring adopted by a stressed mother. The last two groups contained offspring, either unstressed or stressed prenatally, that were adopted by mothers of opposite groups. Thus, one group contained prenatally unstressed rats raised by a stressed foster mother while the other contained prenatally stressed rats adopted by an unstressed foster mother. These groups were used to study of the effects of prenatal stress, to study the effects of adoption per se and its influence on the effects of prenatal stress, and to control for the influence of the experiences of the foster mother on the outcomes of adoption. Maternal behavior was observed in specific procedures. Both foster and biological mothers were removed from their cages for 1 min, and the pups were distributed around the cage. Maternal behavior was observed from the moment the mother was reintroduced into the cage. The parameters recorded were retrieval latency, i.e., time spent by the mother to pick up and to place each pup in the nest over 30 min, and time of contact, measured by the time spent by the mother licking and picking up pups over 15 min. These parameters provide reliable information on maternal behavior and are widely used in studies on laboratory rats.

Postnatal manipulation can also take the form of the classic handling procedure (Meaney *et al.*, 1987). After birth, all the pups were kept together with their respective mother. This manipulation was performed daily from postnatal day 1 to postnatal day 21 (day of weaning). Briefly, pups from each litter were picked up and transferred from their home cage to a cage containing paper toweling. Separate cages were used for each litter throughout the experiment. Pups from one litter remained together in the cage for 15 min (at 11.00 h every day) before being returned to their home cage. The mother was taken out of the home cage, kept alone in another cage over the 15 min and was then returned to the home cage together with her pups. Handling sessions were always performed in the same experimenter.

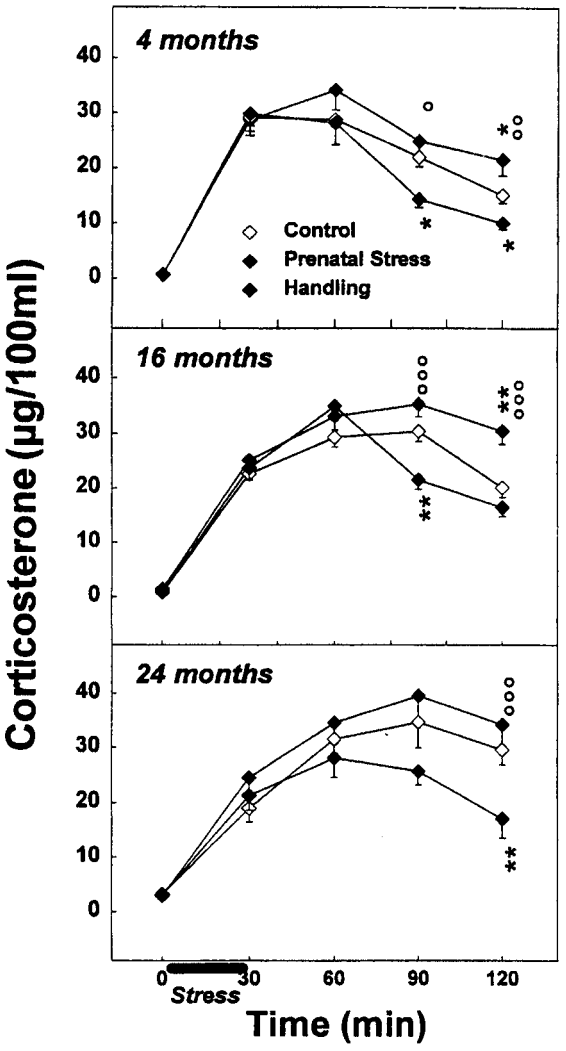

FIGURE 4 Longitudinal study of corticosterone secretion at 4, 16 and 24 months in control (C, n=20), prenatal stress (PS, n=12) and handling (H, n=7) animals. The time course of the secretion of corticosterone is represented at different times following a 30-min restraint stress (black line of abscissa). At 4 and 16 months, the post-stress secretion of corticosterone, at T90 and T120 min, is increased in PS animals in comparison with C and H animals (PS versus C, $^{*}p<0.05$; $^{**}p<0.02$; PS versus H, °p<0.02, °°p<0.01, °°°p<0.001). while the secretion is decreased in H animals compared with C animals ($^{*}p<0.05$, $^{**}p<0.01$). At 24 months the recovery of the response to stress, 2 hrs after the beginning of the stress, differs between groups. The secretion is higher in PS animals than in H animals (°°°p<0.001) while it is lower in H animals than in C animals ($^{**}p<0.01$)

In adults, stress was administered by the restraint stress carried out in an identical plastic cylinder, for 30 minutes), hormone levels being determined in blood samples withdrawn from the tail vein. In some cases rats were placed in circular corridor, a novel environment considered as a stressful situation. The procedure used for hormonal and receptor assays have been extensively described in details (see Maccari *et al.*, 1995). Finally the behavioral measures have been described in Vallée *et al.* (1997, 1999).

III. LONG TERM HORMONAL AND NEUROBIOLOGICAL CHANGES AFTER PERINATAL STRESS

A. Early maturation and feedback defect of the HPA axis

In the adult, the HPA is central for the control of the homeostatic disturbances induced by stress and the hyperactivity of HPA axis has already been associated with behavioral disorders. The activity of the HPA axis plays also a critical role in the behavioral modifications observed in prenatally-stressed rats. Thus, the development of the HPA axis of the fetus is influenced by *in-utero* exposure to abnormal levels of maternal glucocorticoids during stress which are able to cross the placental and blood-brain barriers (Zorsow *et al*, 1970, Maccari *et al.*, 1998) and that results in long lasting perturbations in the offspring. Literature data show that a prenatal stress is able to increase HPA axis reactivity in the early stage of life (Takahashi et a., 1992) but it was not clear if this manipulation was able to modify glucocorticoïd feedback in the adult and, if so, how. Hippocampal type I and type II corticosteroid receptors regulate at least in part the negative feedback of the HPA axis in adult animals (for review, see Mc Ewen *et al*, 1986). We investigated the influence of prenatal stress on the development of the HPA axis regulation and

corticosteroid receptors density of the offspring (Henry *et al.*, 1994).

As show in fig. 1 maternal stress during pregnancy has short- and long-term effects on HPA axis reactivity of the offspring. In 3 and 21-day old male rats, the rise in plasma corticosterone in response to stress was significantly higher in prenatally-stressed pups. Furthermore, control 3 day-old rats showed no response to novelty-stress. In control adult rats corticosterone levels declined at 120 min, whereas prenatally-stressed subjects still displayed elevated levels after the same delay. Moreover, prenatal stress decreased type I and type II corticosterone receptors in the hippocampus at 21 and 90 days of age, whereas the same group studied at 3 days after birth did not display any change in receptor number (fig.2). No change in receptor affinity was encountered in animals examined at 21 and 90 days of age. Both basal and stress corticosterone levels increase during development. Type II hippocampal glucocorticoid receptor density appeared to be greater than type I density at every age and type I and II receptors reached the adult's density at 21 days. Importantly these data evidence a possible plasticity of the stress hyporesponsive period (SHRP), which is mainly based on the lack of corticosterone secretion after exposure to various stressors, as we found in control 3 day-old rats. Our data evidence that 3 day-old animals born by mothers stressed during the last week of pregnancy respond to the stress procedure, and the prenatally-stressed 3 day-old rats had the same density of hippocampal corticosteroid receptors than controls, so that the changes in corticosterone secretion appear earlier than the changes in corticosteroid receptors. This disappearance of the SHRP could account for the decrease in hippocampal glucocorticoid receptor densities observed in prenatally-stressed 21 and 90 day-old rats. In fact, rats treated with glucocorticoids during the first week of life have permanently reduced brain weights and DNA contents and the effects are most profound in those brain regions where there is extensive postnatal mitosis, such as in the hippocampus (Bohn, 1980). Maternal stress alters in the long run the reactivity of the HPA axis in response to stress and decreases the number of type I and II corticosterone receptors in the hippocampus of adult rats.

B. Neuroadaptation within the dopamine transmission and increased psychostimulant actions

In another series of experiments we evidenced that restraint stress resulted in functional alteration in the meso-limbic dopaminergic system in the offspring (Henry *et al.*, 1995). First, prenatal stress induced opposite changes in dopamine D2 and D3 receptor densities in the nucleus accumbens of the adult offspring. The D2 receptor density increased by 24% in the nucleus accumbens, but not in the striatum, while the D3 receptor density decreased in both the shell (-16%) and the core (-26%) of the nucleus accumbens. In contrast, no change in dopamine receptor density was detected in the striatum, and the D1 receptor binding in the nucleus accumbens was not significantly affected by the prenatal stress. Second, these prenatally-stressed animals, with a higher D2 and a lower D3 receptor density in the nucleus accumbens, were more rapidly sensitized to amphetamine, although their motor response to the first injection of amphetamine was comparable to that of the controls, indicating that they were not previously sensitized to amphetamine. Moreover, there was no difference between the prenatally-stressed animal and the controls after the injection of saline, showing that the basal level of locomotor activity was not influenced by prenatal stress A complex literature has been devoted to the involvement of the meso-accumbens dopaminergic system in the effects of psychomotor stimulant drugs, in the sensitization to psychostimulant drugs, and in the self-administration of psychostimulants, which are three related but distinct processes (for review see Le

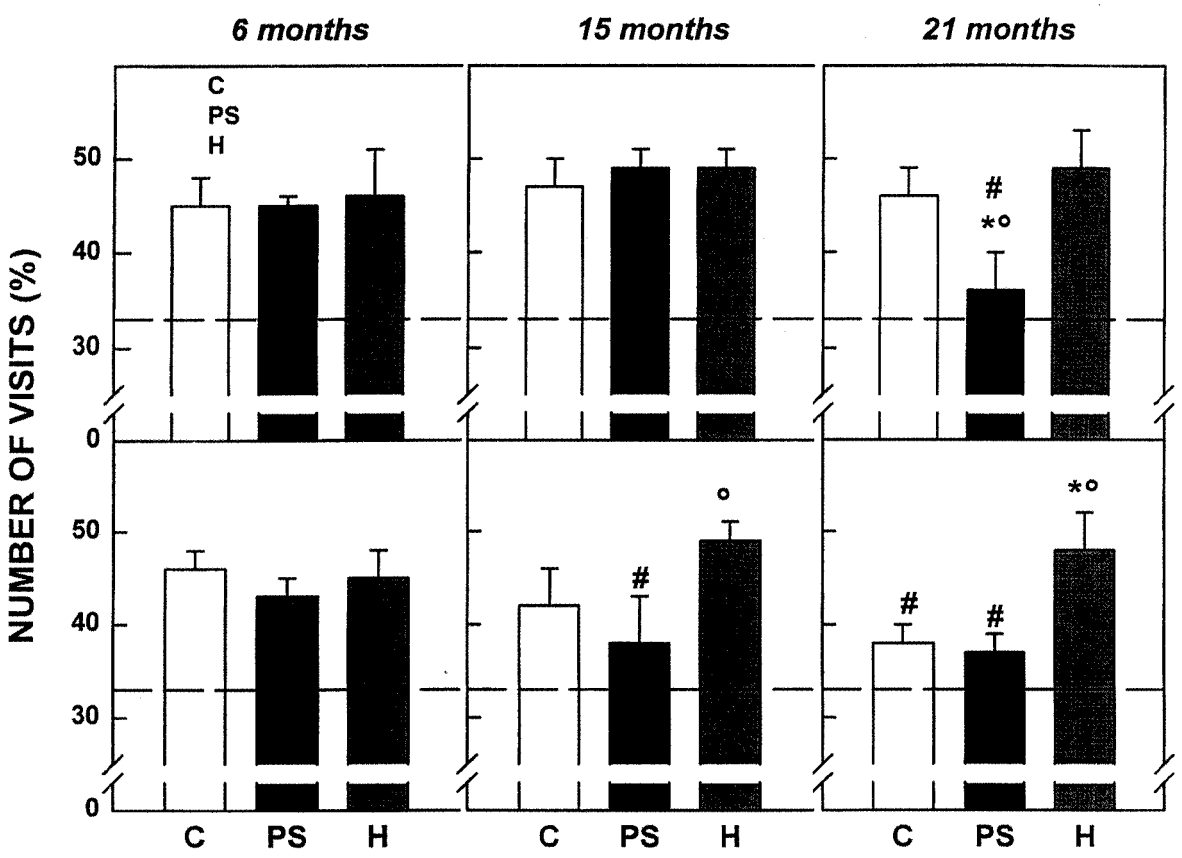

FIGURE 5 Longitudinal study of the spatial recognition memory in the Y maze at 6, 15 and 21 months in control (C, n=20), prenatal stress (PS, n=12) and handling (H, n=7) animals. Top. Percentage of the number of visits to the novel arm with an 8-h intertrial interval (ITI). The performance of PS animals at 21 months is not different from random exploration of the three arms of the maze (33% dotted line), while C and H animals perform significantly better than chance. PS animals perform less well than C and H animals do. PS animals perform less well than C and H animals do. PS animals versus C animals, $^{*}p<0.05$; PS animals versus H animals, $^{\circ}p<0.05$. Bottom. Percentage of the number of visits to the novel arm with a 24-h ITI. The performance of C animals is impaired at 21 months, i.e. they explored the three arms of the maze equally. Prenatal stress increases the age-related deficits, as the performance of PS animals is also impaired at 15 months and remains impaired at 21 months. Conversely, postnatal handling inhibits the age-related deficits. H animals recognize the novel arm throughout their lives, and they perform better than PS animals at 15 months and better C and PS animals at 21 months. H animals versus C animals, $^{*}p<0.05$; H animal versus PS animals, $^{\circ}p<0.05$. #Response at the chance level (33%, three arms)

Moal and Simon, 1991). Taken together, our data suggested of a correlation (and possibly a causal relationship) between a particular pattern of sensitivity to dopamine in the nucleus accumbens (higher D2 and lower D3 receptor density) and a capacity for stimulant sensitization. As we shall see (part V) this accelerated sensitization to psychostimulants could account for the increased propensity of prenatally-stressed rats to develop amphetamine self-administration in adulthood.

C. Corticosterone-dopamine interactions

A potential candidate as mediator of maternal stress effects on the dopaminergic system of the

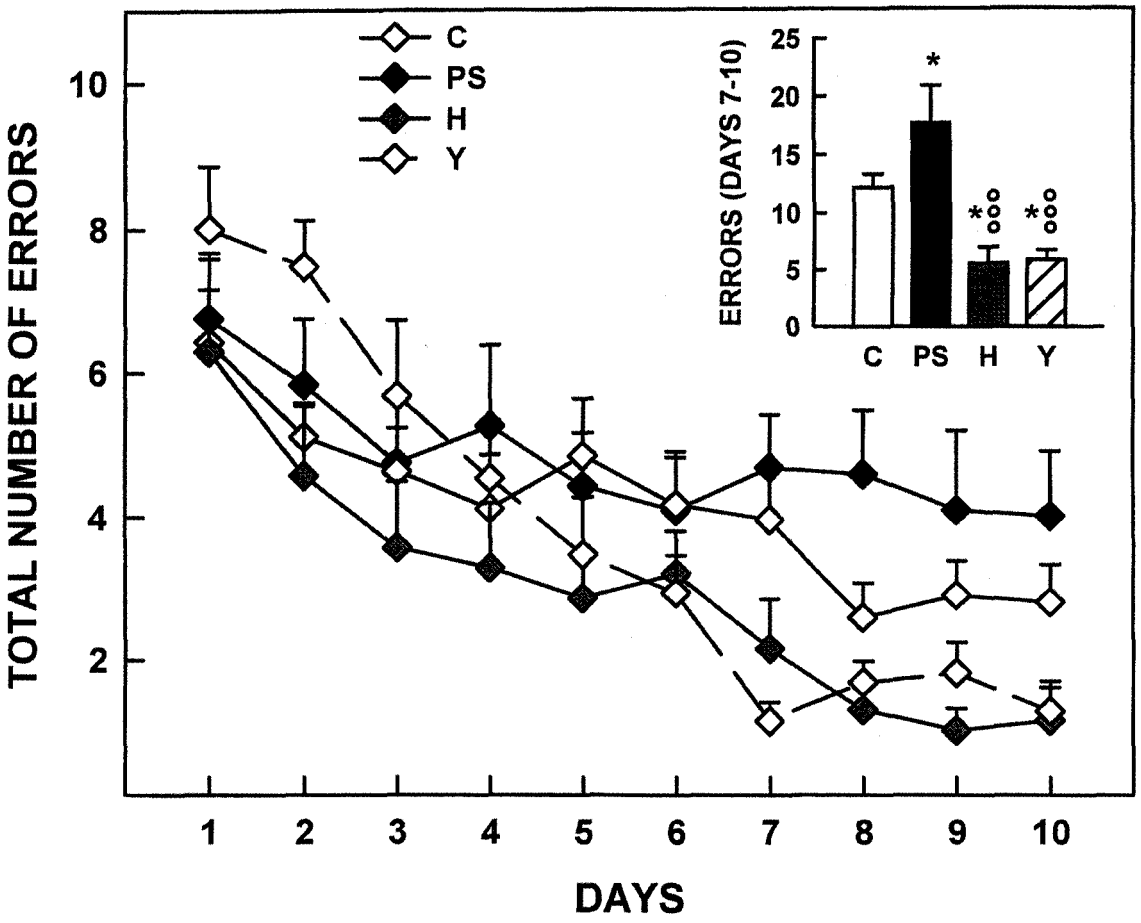

FIGURE 6 Working memory performance in the radial maze in control (C, n=20), prenatal stress (PS, n=12) and handling (H, n=7) animals at 22 months old, and in another young (Y, n=15) control animals at 5 months old. The total number of errors over the last 4 days (days 7–10) of the test is represented in the inset. PS animals made more errors than C animals, while H animals made fewer errors than C and PS animals. Moreover, H animals performed as well as Y animals. PS animals versus C animals. $^{*}p<0.05$; H animal versus C animals, $^{*}p<0.02$; H animals versus PS animals, $^{\circ\circ\circ}p<0.001$; Y animals versus C animals, $p<0.02$; Y animals versus PS animals, $^{\circ\circ\circ}p<0.001$

offspring is an impaired control of corticosterone secretion. As evidenced before, corticosterone released during stress sessions in the mother affects the development of HPA axis in the fetus that persists until adulthood. In another study we have shown that glucocorticoids promote sensitization to amphetamine in rats, mainly through type II receptors (Rivet *et al.*, 1989) while administration of psychostimulant drugs activates the HPA axis; moreover blockade of the HPA axis attenuates amphetamine-induced sensitization without affecting the amplitude of the motor response to the first amphetamine injection (Cole *et al*, 1990), while high circulating levels of corticosterone correlate with an increased propensity to amphetamine self-administration (Piazza *et al*, 1991a). The HPA axis thus plays a key role in the development of sensitization to psychostimulant drugs. This idea is further supported by the presence of glucocorticoid recep-

tors in the dopaminergic neurons, within the ventral tegmental area, projecting to the nucleus accumbens and the observation that glucocorticoids modulate the release of dopamine in the mesolimbic system (Piazza and Le Moal, 1997; Piazza *et al* 1996, Härfstrand *et al*, 1986).

Finally, these experiments provide an animal model in which an epigenetic factor determines individual differences in the ability to develop psychostimulant sensitization, concomitant to changes in mesolimbic dopamine system that may help to understand the neural substrate for vulnerability to drug addiction (part V). For a large part the profound HPA axis disturbances are causal factors for these symptoms.

IV. EMOTIONAL AND COGNITIVE DELETERIOUS CHANGES AFTER PERINATAL LIFE EVENTS : A LIFE-SPAN STUDY. ROLE OF HPA AXIS ALLOSTASIS

A. Emotional reactivity and anxiety

Prenatal stress and postnatal manipulations have been associated with an increase (Fride *et al.*, 1986) and a decrease (Fride and Weinstock, 1988; Wakshalk and Weinstock, 1990), respectively, in emotional behavior. In agreement with these findings, a postnatal manipulation, handling in the first 3 weeks of life, has been reported to prevent the change in behavioral reactivity observed in adult rats previously submitted to a prenatal stress such as restraint stress of the dams during gestation (Wakshlak and Weinstock, 1990) while others failed to confirm these results concerning behavioral reactivity (Pfister and Muir; Ogawa *et al.*, 1994). These differences may be attributable to the use of different early manipulations or different behavioral tests (see Vallée *et al.*, 1997).

We have developed a series of experiments to determine the role of epigenetic factors in behavioral reactivity and emotion (Vallée *et al.*, 1997). The long-term influence of perinatal experiences on adult emotional behaviors and their correlation, as suspected before, with the stress-induced corticosterone secretion has been studied. To this end, two perinatal environmental modifications were used; a prenatal stress, consisting of repeated restraint of the mother during the last week of pregnancy and a postnatal manipulation, consisting of daily handling during the first 3 weeks of life. In the adult offspring of these perinatal manipulations, anxiety-like behavior has been assessed by evaluating behavioral reactivity in response to novelty and anxiety tasks, using several parameters. Furthermore, to discriminate exploratory behavior from escape behavior, a descriptive analysis of these parameters has been performed using a principal component analysis (PCA). Finally, a correlation between these behavioral responses and stress-induced corticosterone secretion in these rats has been investigated.

The results demonstrate that prenatal stress and postnatal handling induce opposite behavioral responses to novelty and opposite neuroendocrine responses to stress in adult offspring. Prenatal stress induced a novelty-induced escape behavior and a prolonged stress-induced corticosterone secretion. The results analysis obtained with the PCA show that the behavioral reactions to novelty can be dissociated in two responses: exploratory and escape. Thus, the increased number of visits in a Y-maze test and increased distance covered in a open-field test during the first 5 min were associated in the same factor of the analysis and was interpreted as an initial escape behavior in response to novelty. Furthermore, prenatally stressed rats spent less time in the open arms of an elevated plus-maze, reflecting an avoidance of anxiogenetic places. The postnatal handling manipulation, in contrast, induced an enhanced exploratory behavior in response to novelty and a reduced stress-induced corticosterone secretion. Indeed, handled rats spent more time in the open arms of the elevated plus-maze (fig.3) and

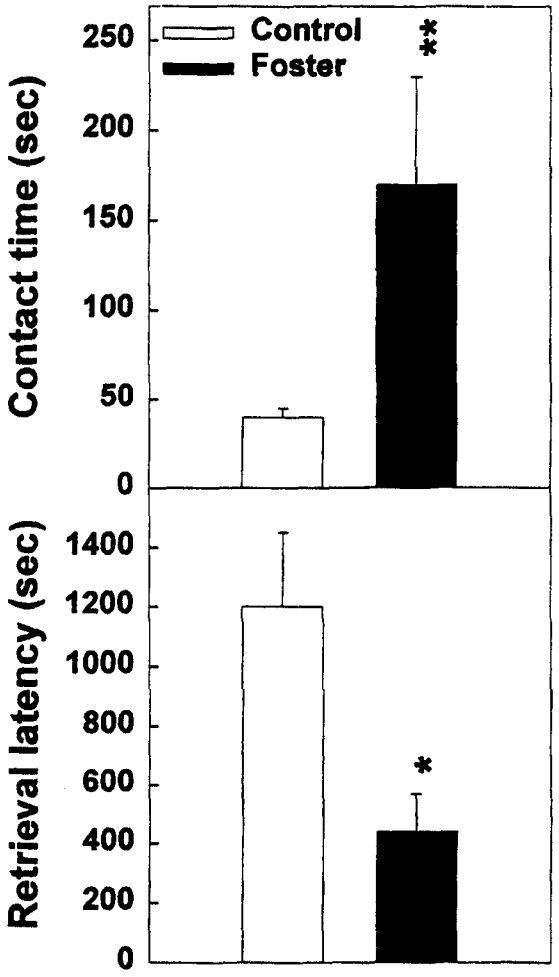

FIGURE 7 Effects of adoption, on day 1 of the adoption procedure, on maternal behavior. Top, Foster mothers (n=15) spent longer licking and picking up the pups (contact time) than did biological mothers (n=20). Bottom, latency to replace all the pups in the nest (retrieval latency) was lower in foster than in biological mothers. The duration of observation was of 15 min for the contact time and 30 min for the retrieval latency. $^{*}p<0.05$; $^{**}p<0.01$. Errors bars show SEM

spent less time in the corners of the open-field test. These two behavioral responses are interpreted as a unique behavior, because they are associated in a PCA analysis. They may represent an exploration of anxiogenic environment, i.e., the center of the open field and the open arms of the elevated plus-maze.

The correlation analysis including all the animals showed that both the number of visits in the Y-maze test during the first 5 min and the time spent in the corners of the elevated plus-maze were positively correlated with the corticosterone secretion after a stress, whereas the time spent in open arms of the elevated plus-maze was negatively correlated with the corticosterone secretion after a stress. In brief our data evidenced that animals with high levels of corticosterone 2 hr after stress, such as prenatally stressed animals, have a high escape behavior, and animals with a reduced corticosterone secretion 2 hr after stress, such as postnatally handled animals exhibits a high exploratory behavior.

These data evidence that the emotional patterns of adults is differentially influenced by perinatal experiences. Prenatal stress induces a hyper-anxiety, expressed as an escape behavior, which is positively correlated with post-stress levels of corticosterone, whereas early postnatal handling induces a hypo-anxiety, expressed as an exploration behavior, negatively correlated with post-stress levels of corticosterone. Prenatal stress induces a prolonged post-stress corticosterone secretion in adult rats associated with a decreased hippocampal corticosteroid receptors. In the other hand, early postnatal handling induces a decrease in corticosterone secretion in response to stress and an increase in the number of hippocampal receptors in adult rats, these effects persisting in aged rats (Meaney *et al.*, 1988). Interestingly, these study show that prenatal and postnatal events had opposite influences on regulation of the HPA axis activity following stress in adulthood.

B. Cognitive evaluation after perinatal stress: a life-span study

In contrast, neither prenatal stress nor handling changed spatial learning and memory performance in adult rats. Indeed, in the water maze, the distance and latency measures did not differ among the groups in the learning and reversal

phases. Moreover, in the two trials memory test, the number of visits and time spent in the novel arm were not different among the groups.

The HPA axis plays a role in cognitive mechanisms. For example, in humans, a negative relationship between stress-induced cortisol levels and memory performance has been reported in healthy adults and administration of glucocorticoid agonists induces memory impairments in humans as well as in animals (for review, see McEwen and Sapolsky, 1995; Kirschbaum *et al.*, 1996; Vallée *et al.* 1997), while glucocorticoids are involved in the regulation of memory storage (McGaugh, 1989). However effect of prenatal and postnatal experiences on cognition has been studied to a lesser extent than anxiety and emotion and the behavioral effects reported are not unequivocally related to cognitive functions.

No study had investigated whether these opposite effects persisted throughout the entire life of the animals. Moreover these data led open the question of the evolution of cognitive abilities in a context of an increased stress axis reactivity through life, leading to allostasis load. As shown, this axis is one of the neurobiological substrates of the behavioral consequences of perinatal stressful events. The glucocorticoid cascade hypothesis (Sapolsky *et al.*, 1986, McEwen and Sapolsky, 1995) postulates that during ageing, glucocorticoids might be involved in cognitive alterations. Thus, elevated circulating glucocorticoids levels are related to memory impairments in elderly subjects (Lupien *et al.*, 1994, 1998), as well as in old rats (Landfield, 1978; Issa *et al.*, 1990). Although these studies pointed to the existence of a subpopulation of aged subjects differing in HPA activity and cognitive efficiency, they did not test for the impact of altered glucocorticoid secretion through life on memory performance in later life. More importantly, in these cross-sectional studies, relationships have been evaluated in different animals across different age ranges and many have focused only on aged rats. So that it was of importance to develop investigations aimed at the understanding of co-evolution of the age-related HPA activity and behavioral alteration.

We investigated the long-term consequences of a prenatal or postnatal stress in rats upon the HPA activity and cognitive performance, with a particular interest in relationships between a hyper- or hypo-secretion of glucocorticoids and the age-related learning and memory performance (Vallée *et al.*, 1999). In brief the data show that prenatal stress and postnatal handling induced opposite neuroendocrine responses to stress throughout the life of the offspring, associated with opposite cognitive effects in later life. In control rats, both basal and stress-induced corticosterone secretion increased with age. The elevated basal secretion was observed in old but not in middle-aged rats. However, the stress response was enhanced in middle-aged rats and further accentuated in the old rats. These results corroborates data reported in humans.

As shown in fig.4 early stressful experiences have opposite influences on the age-related glucocorticoids secretion of the animals. Conversely postnatal handing prevents the age-induced impairment in HPA axis function. The fact that the HPA activities of old control rats and old prenatal stress rats are similar could be explained by a "ceiling effect" due to the age of the animals (Sapolsky, 1992). We also showed that these data were largely related to corresponding changes in hippocampal receptors densities and binding, mainly of type II category. If the mechanisms by which prenatal stress-induced increased in maternal glucocorticoids impairs the offspring axis are well established (Barbazanges *et al.*, 1996a), few is understood for the postnatal effect.

Although the perinatal manipulations had no effect on the learning and memory capacities in young rats, they had a strong impact on the cognitive performance in old animals. Prenatal stress increases risk factors related to ageing and enhances age-related memory impairments. This alteration became apparent in middle-aged, i.e., 16–18 months for rats. Prenatal stress rats exhib-

ited an impaired recognition memory in the Y maze compared with controls. Moreover, the prenatal stress induced further deficits in old rats. This was observed for recognition memory in the Y maze (fig.5) and working memory in the radial maze (fig.6). Conversely, we also observed that postnatal handling can prevent memory deficits in old rats in the Y maze and radial maze. No deficits in recognition memory of the novel arm in the Y maze with a 24-h intertrial interval were observed for the aged handled rats in contrasts to the aged control rats who explored the three arms of the maze at random. In addition, in the radial maze the aged handled animals made significantly fewer errors than did the aged controls. Interestingly, the memory performance of aged handled rats did not differ from that of young control naive rats. These results strongly suggest that age-related learning and memory deficits can be prevented by postnatal handling. Taken together these results indicate that perinatal manipulations failed to alter the spatial memory function at 6–7 months old. The difference emerged over time as a function of an interaction with age risk factors. Thus, the differences observed in memory performance could be explained by an inhibition of the ageing process induced by postnatal handling, while the prenatal stress increased this process.

In summary, our results provide evidence that environmental manipulations occurring early in life induce changes in the HPA axis activity that endure throughout the life (allostasis load) of the organism and occur before effects on cognitive functions. These results suggest that prenatal stress could be a useful model for studying age neurodegeneration, especially for understanding mechanisms underlying the role of glucocorticoids in cognitive disorders.

C. Interactions between pre and postnatal events

Although prenatal and postnatal events can have different behavioral consequences, they may also impinge on the same behavioral response, and postnatal manipulations can reverse the behavioral effects of prenatal stress. For example, postnatal handling can reverse the increase in emotional reactivity induced by prenatal and reduces stress-induced corticosterone secretion in adult and aged individuals, probably by strengthening corticosterone feedback. It was of interest to examine the influence of postnatal experiences or prenatal stress deleterious effects.

We thus assessed stress-induced corticosterone secretion and hippocampal corticosteroid receptors in adult rats that had been submitted to prenatal and/or postnatal manipulations. Again repeated restraint of the mother during the last week of pregnancy was used as prenatal stressor, while adoption at birth was used to change the postnatal environment. Adoption is, in our hands, another way to stimulate the mother -offspring diadic relationship and an consequence to stimulate the pups with a minor intervention of the experimenter, than through handling procedure. Measures of mother's behavior evidence that foster mothers displayed more contact time and lickings with the pups and far less retrieval latencies after separation (fig.7). As explained before (past II), such experiments required a complex design with several experimental groups in order to evaluate the role of each components, stress, state of the mothers, adoption, and interactions. Our results (Maccari *et al.*, 1995) demonstrate (fig.8) that 1) prenatal stress decreases central corticosteroid receptors, and prolongs stress-induced corticosterone secretion in adult male rats, 2) adoption at birth, independently by the stress experience of the foster mother, reverses the effects of prenatal stress, 3) adoption per se modifies maternal behavior, increasing pup-directed behavior in foster mothers, and decreases the stress-induced corticosterone secretion peak in the adult offspring. The interaction of adoption with prenatal stress and the biological effects of adoption *per se* were not influenced by the treatment received by

adoptive mothers during pregnancy (not shown). Similar results were observed whether the foster mother was stressed or not during pregnancy. Adoption also enhanced maternal behavior as the foster mothers devoted more attention to the pups than did the biological mothers.

In conclusion these data demonstrate the complexity of environmental actions when they occurred at different periods of development. These actions are long-lasting anf might be at the source of neurodegenerative processes observed during aging. Importantly, some of these environmental actions might have protective effects.

V. PROPENSITY FOR INTRAVENOUS PSYCHOSTIMULANT SELF-ADMINISTRATION IN ADULT OFFSPRING OF STRESSED MOTHERS

Although recent years have seen a significant change for the understanding of the neurobiological substrates of dependence, the psychobiological determinants of drug addiction are still largely unknown. However, clinical and psychological studies indicate that one of the main factors conditioning the development of addiction is the peculiar sensitivity of some individuals to the reinforcing effects of these addictive drugs. Comprehension of the origin of such differences should, therefore, throw light on the etiology of addiction (for review, Koob and Le Moal, 1997). In brief why some individual will succomb and others not, why some organisms are more vulnerable is still unknown.

In previous studies using intravenous drug self-administration (SA), a widely used experimental model of drug addiction, we found that laboratory animals exhibited important individual differences to self-administer drug of abuse. At low drug doses, only some rats developed SA. These animals were characterized by three main features. First, they had functional imbalances in the mesocorticolimbic dopaminergic (DA) network, reflected by higher DA utilization in the nucleus accumbens and a lower utilization in the prefrontal cortex (Piazza *et al*, 1991b). Second, they had a higher behavioral and endocrinological reactivities to stress with a higher locomotor reactivity and a longer corticosterone secretion in response to exposure to a mild stress novelty (Piazza *et al.*, 1991a). The longer corticosterone secretion showed by these animals was due to a lower affinity of hippocampal corticosteroid receptors. Third, they had a higher locomotor reactivity to an intravenous or intraperitoneal injection of psychostimulant (Piazza *et al*, 1991c).

Given these pathophysiological determinants, it was of interest to investigate whether offspring of stressed mothers were more vulnerable to drug addictive effects, and in the same time, to contribute to open a new window on the controversial problems concerning the origins of individual vulnerabilities and subsequent predispositions to enter in an addictive cycle (Koob and Le Moal, 1997). It is well established that exposure of adult animals to stress profoundly influence the predisposition to self-administer drugs (for review, Piazza and le Moal, 1998). Moreover observations suggest that prenatal stress could have an influence on amphetamine self-administration. Prenatal stress has been found to have long-term effects on the activity of the DA system and on DA-related behaviors (Moyer *et al*, 1978; Fride and Weinstock, 1989). Moreover, we have evidence that prenatal stress increases and prolongs corticosterone secretion in response to stress (Henry *et al.*, 1994).

We studied (Deminière *et al*, 1992) SA in the offspring of mothers submitted to a restraining procedure during the last week of pregnancy. These animals were also tested for locomotor reactivity to novelty and to stimulant, since these behaviors are characteristically enhanced in animals spontaneously predisposed to SA (Piazza *et al*, 1989). In brief, (see Deminière and al., 1992, for methods) animals from control, non stressed

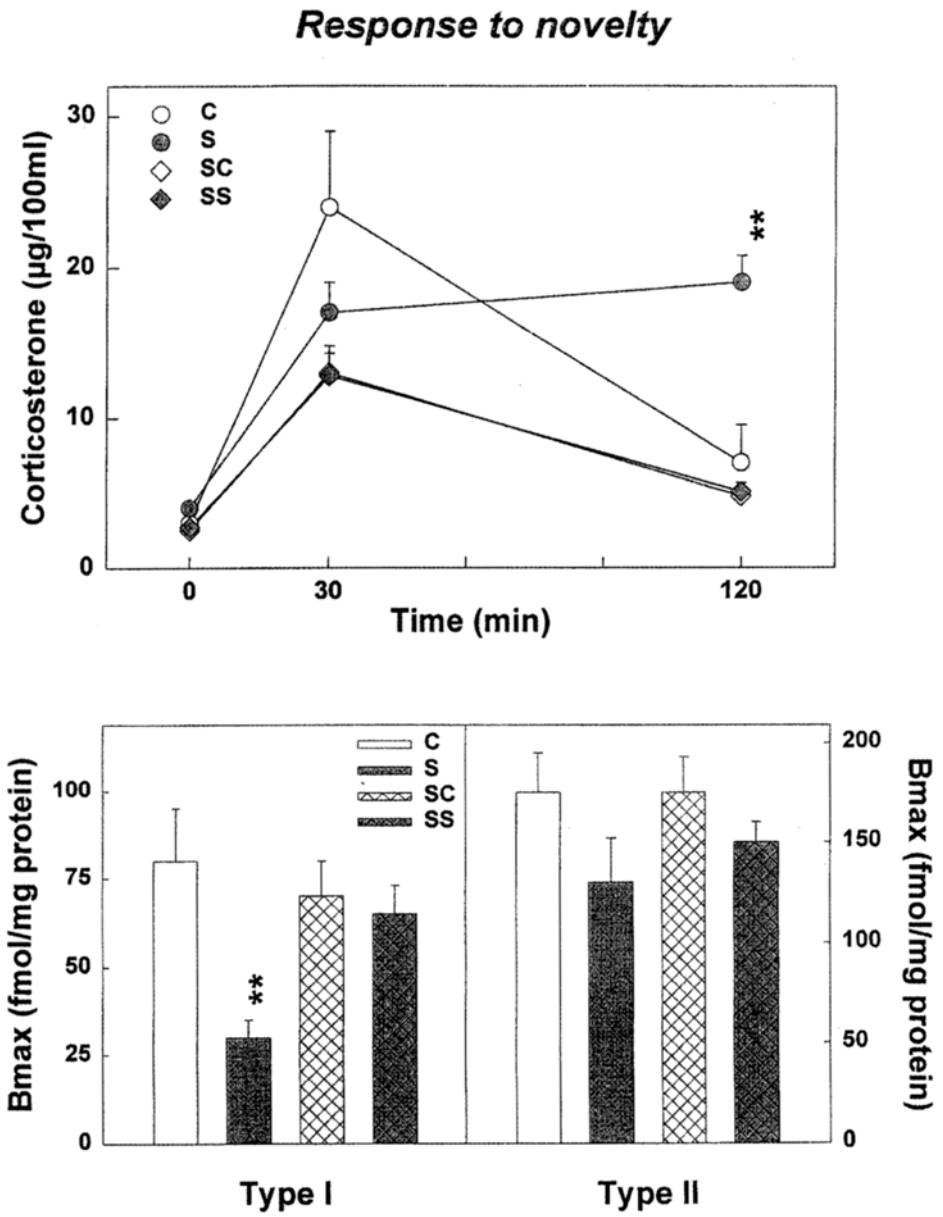

FIGURE 8 Plasma corticosterone secretion after novelty exposure (top) and type I and type II (B_{max}) corticosteroid receptors (bottom) in adult prenatally unstressed rats raised by their biological mother (C, n=7), adult prenatally stressed rat raised by their biological mother (S, n=6), adult prenatally stressed rats adopted by a control unstressed mother (SC, n=5), and adult prenatally stressed rats adopted by a mother stressed during pregnancy (SS, n=6). Top: Prenatally stressed animals (S) displayed higher corticosterone levels than those of those of control rats (C) after 120 min of novelty exposure. Animals that were both stressed and adopted did not differ from controls, either if the adoptive mother was unstressed (SC) or stressed (SS) during pregnancy. Bottom: Type I corticosteroid receptors were reduced by prenatal stress and this effect was totally reversed by adoption in both SC and SS groups. Neither prenatal stress nor adoption significantly modified type II corticosterone receptors. The affinities of type I or type II receptors were not influenced by any of the experimental conditions studied. $^{**}p<0.01$ (prenatal stress vs control). Error bars show SEM

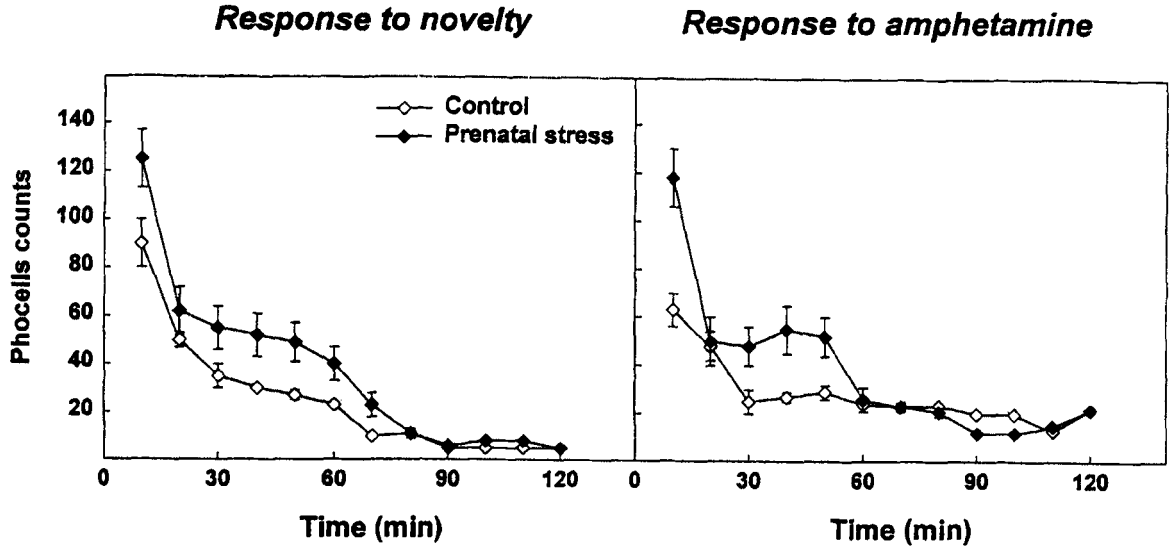

FIGURE 9 Left: Effect of prenatal stress on the locomotor response to novelty. Compared to control animals (Control, n=18) the prenatal stress rats (Prenatal Stressed, n=14) showed a higher locomotor response to novelty (P=0.02). Right: Effect of prenatal stress on the locomotor response to amphetamine 0.3 mg/kg i.v.). Control and prenatal stress group differed in their response to amphetamine over time (P<0.001). The prenatal stress group showed a higher locomotor response (P=0.01) during the first hour of testing

mothers, and from stressed mothers groups were implanted with intracardiac catheters. A low dose of amphetamine was used, which had been found to discriminate between animals with different propensities to self-administer amphetamine (Le Moal *et al*, 1979). A logarithmic transformation was used to normalize the distribution of raw data of self-administration. The total activity of prenatal-stressed animals was approximately 50% higher than that of the controls. Prenatal stress animals also had a increased locomotor reactivity to amphetamine (fig. 9). The prenatal stressed animals showed a higher locomotor reactivity to amphetamine over the first hour of testing. Prenatal stress was found to induce a faster response to amphetamine. In the first 10 min after the injection, the response of the stressed group was nearly double that of the controls. Furthermore, prenatal stress influenced the propensity to develop amphetamine self-administration (fig. 10). While control and stressed animals did not differ during the first day of testing, animals in the prenatal stress group showed a higher intake of amphetamine on subsequent days. The two groups of animals did not differ for the number of nose-pokes in the inactive hole and both groups made, over the 5 days of testing, more nose-pokes in the active hole that in the inactive one.

As noticed before, modifications of the activity of the dopaminergic (DA) system may account for the behavioral changes induced by our stress procedure. Several classic observations support this idea (for review: Le Moal and Simon, 1991). DA projections to the nucleus accumbens are thought to be the major neurophysiological substrate of the response to novelty and amphetamine-induced locomotor behaviors and psychostimulants SA. Moreover, animals that

are spontaneously predisposed to develop amphetamine self-administration have higher DA activity in the nucleus accumbens. Finally, prenatal stress may modify the activity of the DA system in the prefrontal cortex and in the nucleus accumbens. Although the DA system is a good candidate for the neurobiological substrate of prenatal stress action, the involvement of other systems cannot be ruled out. Indeed, other neuronal systems, such as the GABAergic and serotoninergic are modified by prenatal stress and may influence the response to amphetamine.

Finally, whatever the neurotransmitters involved, dopamine being a good candidate, early stress axis deregulation might be the primary cause of these deleterious effects.

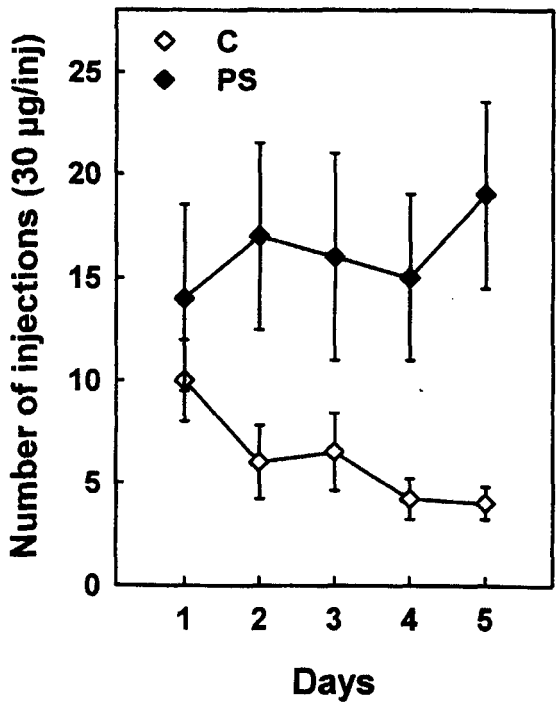

FIGURE 10 Influence of prenatal stress on amphetamine self-administration (30 µg/injection). Prenatal stress animals (PS, n=14) significantly increased the intake of amphetamine over the 5 days of testing (P=0.03), compared to control (C, n=17)

VI. CONCLUSION

Although the development of an organism carries a strong genetic component, its early environment has long lasting influence. Both components shape psychobiological temperaments and are at the origin of individual differences. Moreover, both components can equally at the origin of vulnerabilities for ulterior deleterious life events, and at the origin of neurodegenerative processes.

Both prenatal and postnatal events may modify the activity of the HPA axis, albeit in opposite directions, and early postnatal adoption has been found to suppress the biological effects of prenatal stress, probably by increasing maternal behavior. Our results also show the major role played by maternal glucocorticoids on the development of endocrine function in the offspring. In fact, high level of maternal glucocorticoids during prenatal stress has marked long-term repercussions on the efficiency of the offspring's HPA negative feedback mechanisms. The recognized influence of HPA axis activity on behavioral adaptation suggests that a modification of corticosterone secretion could be a biological substrate of the long-term behavioral effects of prenatal and postnatal events.

Finally the data presented illustrate the fact that, beyond homeostasis, when the organism is subjected to non-controlled pressures, an allostasis state develops that has its our logic : a new equilibrium that is not health anymore, but vulnerability to disease.

References

Armstrong, K.L., O'Donnell, H., McCallum,R., Dadds, M. (1998) Childhood sleep problems: association with prenatal factors and maternal distress/depression. *J. Paediatr. Child. Health*, **34**, 263–6.

Barbazanges, A., Piazza, P.V., Le Moal, M. and Maccari, S. (1996a) Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. *J. Neurosci.*, **16**, 3943–3949.

Barbazanges, A., Vallée, M., Mayo, W., Day, J., Simon, H., Le Moal, M., and Maccari, S., (1996b) Early and later adop-

tions have different long-term effects on male rat offspring. *J. Neurosci.*, **16**, 7783–7790.

Barden,N., Reul, J.M.H.M., Holsboer, F. (1995) Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? *Trends Neurosci.*, **18**, 6–11.

Bohn, M.C. (1980). Glucocorticoid induced teratologies of the nervous system. In: Yauci J. ed. Neurobehavioral teratologies of the nervous system. pp.365–387. Elsevier, Amsterdam.

Cole, B.J., Cador, M., Stinus, L.., Rivier, C., Rivier, J., and Vale, W., Le Moal, M., and Koob, G.F. (1990) Critical role of the hypothalamo-pituitary adrenal axis in amphetamine-induced sensitization of behavior *Life Sci.*, **47**, 1715–1720.

Copper, R.L., Goldenberg, R.L., Das, A., Elder, N., Swain, M., Norman, G., Ramsey, R., Cotroneo, P., Collins, B.A., Johnson, F., Jones, P., Meier, A.M. (1996) The preterm prediction study : maternal stress associated with spontaneous preterm birth at less than thrirty five weeks gestation. Am. J. Obstet. Gynecol., 175, 1286–1292.

Deminière, J.M., Piazza, P.V., Guegan, G., Abrous, N., Maccari, S., Le Moal, M., and Simon, H. (1992) Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. *Brain Res.*, **586**, 135–139.

Fride, E., and Weinstock, M. (1988) Prenatal stress increases anxiety related behavior and alters cerebral lateralization of dopamine activity. *Life Sci*, **42**, 1059–1065.

Fride, E., and Weinstock, M. (1989) Alteration in behavioral and striatal dopamine asymmetries induced by prenatal stress. *Pharmacol. Biochem. Behav*, **32**, 425–430.

Fride, E., Dan, Y., Feldon, J., Havely, G., and Weinstock, M. (1986) Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. *Physiol. Behav.*, **37**, 681–687.

Glover, V. (1997) Maternal stress or anxiety in pregnancy and emotional development of the child. *Br..J Psychiatry*. **171**, 105–6.

Hammen, C., Davila, J., Brown, G., Ellicott, A., Gitlin, M. (1992) Psychiatric history and stress: predictors of severity of unipolar depression. *J. Abnorm. Psychol.*, **101**, 45–52.

Härfstrand, A., Fuxe, K., Cintra, A., Agnati, L.F., Zini, I., Wilkström, A.C., Okret, S., Zhao-Ying, Y., Goldstein, M., Steinbush, H., Verhofstad, A., and Gustafsson, J.A. (1986) Glucocoticoid receptor immunoreactivity in monoaminergic neurons in the rat brain. *Proc. Natl. Acad. Sci. USA*, **83**, 9779–9783.

Hedegaard, M., Henriksen, T.B., Sabroe, S., Secher, N.J. (1993) Psychological distress in pregnancy and preterm delivery. *British Med. J.*, **307**, 234–239.

Henry, C., Guegant, G., Cador, M., Arnauld, E., Arsaut, J., Le Moal, M., and Demotes-Mainard, J. (1995) Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbeus. *Brain Res.*, **685**, 179–186.

Henry, C., Kabbaj, M., Simon, H., Le Moal, M., and Maccari, S., (1994) Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *J. Neuroendocrinol.*, **6**, 341–345.

Huttunen, M.O., Niskanen, P. (1978) Prenatal loss of father and psychiatric disorders. *Arch. Ge. n Psychiatry*, **35**, 429–31.

Issa, A.M., Rowe, W., Gauthier, S., and Meaney, M.J. (1990) Hypothalamicpituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *J. Neurosci.*, **10**, 3247–3254.

Joffe, J.M. (1965) Genotype and prenatal and premating stress interact to affect adult behavior in rats. *Science*, **150**, 1844–1845.

Joffe, J.M. (1969) Prenatal determinants of behavior. Oxford, Pergamon Press.

Jones, F.N., Tauscher, J. (1978) Residence under an airport landing pattern as a factor in teratism. *Arch. Environ. Health*, **33**, 10–12.

Kirschbaum, H., Wolf, O.T., May, M., Wippich, W., and Hellhammer, D.H., (1996) Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci.*, **58**, 1475–1483.

Koob, G.F., and Le Moal, M. (1997). Drug abuse : hedonic homeostatis dysregulation. *Science*, **278**, 52–58.

Landfield, P.W., (1978) An endocrine hypothesis of brain aging and studies on brain-endocrine correlations and monosynaptic neurophysiology during aging. In Finch, CE, Potter, D.E. and Kenny. A.D. (eds) Aging and Neuroendocrine Relationships. Plenum Press, New York, pp.179–189.

Le Moal, M., and Simon, H (1991). Mesocorticolimbic dopaminergic network: Functional and regulatory roles. *Physiol. Rev.*, **71**, 155–234.

Le Moal, M., Stinus, L., and Simon, H. (1979) Increased sensitivy to (+) -amphetamine self-administered by rats following mesocorticolimbic dopamine neurones destruction. *Nature*, **280**, 156–158.

Lekman, J.F. (1999) Incremental progress in developmental psychopathology: simply complex. Am. J. Psychiatry, 156, 1445–1498.

Levine, S. (1962) Plasma free corticosteroid response to electric shock in rats stimulated in infancy. *Science*, **135**, 795–796.

Levine, S., and Lewis, G.W. (1959) Critical period for the effects of infantile experience on maturation of stress. *Science*, **129**, 42–43.

Levine, S., Haltmeyer, G., Karras, G., and Denenberg, V.H. (1967) Physiological and behavioral effects of infantile stimulation. *Physiol. Behav.*, **2**, 55–59.

Lou, H.C., Hansen, D., Nordenfoft, M., Pryds, O., Jensen, F., Nim, J., Hemmingsen, R. (1994) Prenatal stressors of human life affect fetal brain development. *Dev. Med. Child. Neurol.*, **36**, 826–832.

Lupien, S., Lecours, A.R., Lussier, I., Schwartz, G., Nair, N.P.V., and Meaney, M.J. (1994) Basal cortisol levels and cognitive deficits in human aging. *J. Neurosci.*, **14**, 2893–2903.

Lupien, S., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N.P.V., Mc Ewen, B.S., Hauger, R.L., and Meaney, M.J. (1998) Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neurosci.* **1**, 69–73.

Maccari, S., Piazza, P.V., Kabbaj, M., Barbazanges, A., Simon, H., and Le Moal, M. (1995). Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *J. Neurosci.*, **15**, 110–116.

Maccari, S., Barbazanges, A., Kabbaj, M., Piazza, P.V., and Le Moal, M. (1998) Long-term influences of perinatal life events on behavioral and biological responses to stimuli: role of the mother. In: New frontiers in stress research, modulation of brain function. A.L., E. Grayer, D. Ben-Nathan, E. R. de Kloet (Eds), Harwood academic publishers gmbh, pp.141–154.

Mc Gaugh, J.L. (1989). Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. *Ann. Rev. Neurosci.*, **12**, 255–287.

McEwen, B.S. (1998) Protective and damaging effects of stress mediators. *New Engl. J. Med.*, **338**, 171–179.

McEwen, B.S., and Sapolsky, R.M. (1995). Stress and cognitive function. *Curr. Opin. Neurobiol.*, **5**, 205–216.

McEwen, B.S., De Kloet, E.R., and Rostène, W. (1986). Adrenal steroid receptors and actions in the nervous system. *Physiol Rev.*, **66**, 1121–1188.

Meaney, M.J., Aitken, D.H., Sapolsky, R.M. (1987) Thyroid hormones influence the development of hippocampal glucocorticoid receptors in the rat: a mechanism for the effects of postnatal handling on the development of the adrenocortical stress response. *Neuroendocrinology*, **47**, 278–283.

Meijer, A. (1985) Child psychiatric sequelae of maternal war stress. *Acta Psychiatr. Scand.*, **72**, 505–511.

Moyer, J.A., Herrenkohl, L.R., and Jacobowitz, D.M. (1978) Stress during pregnancy: effect on catecholamines in discrete brain regions of offspring as adults. *Brain Res.*, **144**, 173–178.

Ogawa, T., Mikuni, M., Kuroda, Y., Muneoka, K., Mori, M.J., and Takahashi, K. (1994). Periodic maternal deprivation alters stress response in adult offspring, potentiates the negative feedback regulation of restraint stress-induced adrenocortical response and reduces the frequencies of open field-induced behavior. *Pharmacol. Biochem. Behav.*, **49**, 961–967.

Pagel, M.D., Smilkstein, G., Regen, H., and Montano, D. (1990) Psychosocial influences on new born outcomes: a controlled prospective study. *Social Science Medecine*, **30**, 597–604.

Perkin, M.R., Bland, J.M., Peacock, J.L., Anderson, H.R. (1993) The effect of anxiety and depression during pregnancy on obstetric complications. *B.r J. Obstet. Gynaecol.*, **100**, 629–34.

Pfister, H.P., and Muir, J.L. (1992). Prenatal exposure to predictable and unpredictable novelty stress and oxytocin treatment affects offspring development and behavior in rats. *Int. J. Neurosci.*, **62**, 227–241.

Piazza, P.V., and Le Moal, M. (1997) Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. *Brain Res. Rev.*, **25**, 359–372.

Piazza, P.V., and Le Moal, M. (1998) The role of stress in drug self-administration. Trends Pharmacol. Sci., **19**, 67–74.

Piazza, P.V., Deminière, J.M., Le Moal, M., and Simon, H. (1989) Factors that predict individual vulnerability to amphetamine self-administration, *Science*, **245**, 1511–1513.

Piazza, P.V., Maccari, S., Deminière, J.M., Le Moal, M., Mormède, P., and Simon, H. (1991a) Corticosterone levels determine individual vulnerability to amphetamine self-administration, Proc. Natt. Acad. Sci USA, **88** 2088–2092.

Piazza, P.V., Rouge-Pont, F., Deminière, J.M., Kharouby, M., Le Moal, M. and Simon, H. (1991b) Dopaminergic activity is reduced in the prefontal cortex and increased in the nucleus accumbeus of rats predisposed to develop amphetamine self-administration, *Brain Res.*, **567**,169–174.

Piazza, P.V., Deminière, J.M., Maccari, S., Le Moal, M., Mormède, P., and Simon, H. (1991c) Individual vulnerability to drug self-administration: action of corticosterone on dopaminergic systems as a possible pathophysiological mechanism. In P. Wilner and J Scheel-Krüger (Eds.), The Mesolimbic Dopamine System: From Motivation to Action, pp. 473–495.

Piazza, P.V., Rouge-Pont, F., Deroche, V., Maccari, S., Le Moal, M., and Simon H. (1996) Glucocorticoids have state-dependent stimulant effects on mesencephalic dopaminergic transmission. Proc. Nat. Acad. Sci. USA, **93**, 8716–8720.

Rivet, J.M., Stinus, L., Le Moal, M., and Mormède, P. (1989) Behavioral sensitization to amphetamine is dependent on corticosteroid receptor activation. *Brain Res.*, **498**, 149–153.

Sapolsky, R.M. (1992) Stress, the Aging Brain, and the Mechanisms of Neuron Death. MIT Press, Cambridge, MA, USA.

Sapolsky, R.M., Krey, L.C., and McEwen, B.S. (1986) The neuroendocrinology of stress and aging : the glucocorticoid cascade hypothesis. *Endocr. Rev.*, **7**, 284–301.

Schatzberg, A.F., and Nemeroff, C.B., (eds) (1995) The textbook of psychopharmacology (APA, Washington, DC).

Shell, L.M. (1981) Environmental noise and human prenatal growth. *Am. J. Physiol Anthropol.*, **56**, 63–70.

Sjostrom, K., Valentin, L., Thelin, T., Marsal, K. (1997) Maternal anxiety in late pregnancy and fetal hemodynamics. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **74**, 149–55.

Stott, D.N. (1973) Follow-up study from birth of the effects of prenatal stress. *Dev. Med. Child. Neurol.*, **15**, 770–787.

Vallée, M., Mayo, W., Dellu, F., Le Moal, M., Simon, H., and Maccari S. (1997) Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring : correlation with stress-induced corticosterone secretion. *J. Neurosc.*, **17**, 2626–2636.

Vallée, M., Maccari, S., Dellu, F., Simon, H., Le Moal, M., and Mayo, W. (1999). Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: a longitudinal study in the rat. *Europ. J. Neurosci.*, **11**, 2906–2916.

Wakshlak, A., and Weinstock, M. (1990). Neonatal handling reverses behavioral abnormalities induced in rats by prenatal stress. *Physiol. Behav.*, **48**, 289–292.

Ward, I.L. (1972) Prenatal stress feminizes and desmasculinizes the behavior of males. *Science*, **175**, 82.

Ward, I.L. (1984) The prenatal stress syndrome: current status. *Psychoneuroendocrinology*, **9**, 3–11.

Ward, I.L., and Weisz, J. (1984) Differential effects of maternal stress on circulating levels of corticosterone, progesterone and testosterone in male and female rat fetuses and their mothers. *Endocrinol.*, **114**, 1635–1644.

West, M.J., King, A.P. (1987) Settling nature and nurture into an ontogenetic niche. *Dev. Psychobiol.*, **20**, 549–62.

Zarrow, M.X., Philpott, J.E., and Denenberg, V.H., (1970). Passage of 14C-4 Corticosterone from the rat mother to the fœtus and neonate. *Nature*, **226**, 1058–1059.