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Opiate Agonist-Induced Changes in Behavioral Sensitivity to Clonidine Are Observed in Perinatally Malnourished Rats Exposed to Chronic Stress

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KELLER, E. A., A. REY, A. C. GUTIERREZ AND L. M. CANCELA. *Opiate agonist-induced changes in behavioral sensitivity to clonidine are observed in perinatally malnourished rats exposed to chronic stress.* PHARMACOL BIOCHEM BEHAV **60**(1) 1–5, 1998.—Sensitivity of alpha$_2$-adrenoceptors following repeated immobilization sessions plus morphine (MOR) or β-endorphin (BETA) was assayed by examining clonidine (CLO)-induced hypoactivity in adult malnourished rats at perinatal age. As previously described, chronic restraint did not attenuate the hypoactivity elicited by CLO in malnourished rats, although chronic restraint did have such an effect on motor activity in control animals. MOR and BETA administration prior to each restraint session induced subsensitivity of alpha$_2$-adrenoceptors in malnourished rats as determined by a blunted response to clonidine challenge. An injection of naloxone (NAL) prior to BETA before each stress session fully antagonized the subsensitivity to clonidine observed in malnourished animals. A possible deficiency in the functional role of the opiate system in the process of adaptation to chronic stress in perinatal malnourished rats is suggested. © 1998 Elsevier Science Inc.

Perinatal malnutrition Alpha$_2$-adrenoceptors Chronic stress Opiate agent

EARLY malnutrition leads to several behavioral disturbances in adulthood. Accordingly, behavioral studies have shown an alteration in the responsiveness to stress in perinatally malnourished animals (2,3,9,17,24–26). It has recently been proposed that adaptative changes in monoaminergic receptors may be involved in the mechanisms of adaptation and resistance to stress (5õ7,16,20,28–30). Thus, different types of repeatedly presented stressors evoke a downregulation of brain beta-adrenoceptors as well as a diminished response to cyclic AMP accumulation stimulated by noradrenaline (28–30). Similarly, behavioral observations have indicated that reduced sensitivity of presynaptic dopaminergic and alpha$_2$-adrenoceptors, as well as an increased sensitivity of 5-HT sites, may occur following chronic but not acute immobilization (5–7). Rats malnourished in early life did not develop these adaptive changes in monoaminergic receptors sensitivity following successive stress exposures (14,15). It has been suggested that these adaptive changes in monoaminergic receptors may play a role in the maintenance of normal behaviors after exposure to stressful or aversive events. Thus, as we have previously suggested (13–15), the abnormal response to aversive experiences observed in malnourished rats could be defined as an altered reaction to a stressful situation. It has been repeatedly reported that endogenous opiates play a modulatory role in the development of adaptive changes to chronic stress (4,6,7). Thus, it has been reported that NAL pretreatment fully antagonizes alpha$_2$ and 5-HT$_1$ receptor adaptations following exposures to chronic stress (6,7). Furthermore, treatment with MOR or BETA before each restraint session accelerates the onset of adaptive responses in monoamine receptors (7). In previous work from our laboratory (15), combined treatment using stress and MOR in malnourished rats elicited adaptive changes in 5-HT$_1$ receptors. Consequently, NAL pretreatment abolished the MOR-induced effects on 5-HT$_1$ receptors. These

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results have led us to postulate that early malnutrition may impair the activation of an opiate mechanism involved in the response to aversive experiences. In accordance with this view, it has been reported that adult rats subjected to protein undernutrition in early life (deprivation schedule similar to ours) manifest a reduced release of endorphins following shock or novel training procedures (21,22,31). Other investigators employing two different methods of postnatal malnutrition (rotation of pups between lactating and nonlactating females, expansion of litters (8,27), have reported an altered response to opiate agonists in these animals in adulthood. Because both of these methods involve stressful situations in early life (e.g., maternal separation stress, cooling), and maternal isolation elicits an endogenous opiate response (12), the altered opiate responsiveness observed in these animals in adulthood has been attributed to early experience factors associated with malnutrition manipulations (8,27). Even though there is evidence that the protein malnutrition scheme followed in our lab does not alter the mothering behavior between undernourished and well-nourished rats (10,19), the possibility that such an alteration could happen cannot be fully discarded. Apart from malnutrition-induced impairment in the activation of opioid mechanisms that may be involved in the response to aversive experiences, previous results from our lab indicated that the association of MOR and stress induced the adaptations in 5-HT_1 receptors in undernourished rats. Therefore, it is likely that combined treatment with an opioid agonist and stress could influence the adaptive response to the $alpha_2$-receptors after chronic stress in adult rats undernourished at perinatal age. Persuant to these hypotheses, the influence of combined treatment with either MOR or BETA together with stress on the behavioral response induced by CLO was studied. In another manipulations, each immobilization session was preceded by NAL (opioid antagonist) before BETA, and the behavioral response induced by CLO was evaluated.

METHOD

Deprivation Schedule

A protein deprivation schedule, such as the one previously described (18), was used. Briefly, female rats (Wistar strain) were divided into two groups at 14 days of pregnancy and fed with isocaloric diets containing 24% casein (control group) and 8% casein (experimental group). Diets contained 4 g/kg DL-methionine. After weaning (30 days), pups continued to consume the same diet as their dams until 50 days of age. Both groups were thereafter given balanced standard chow for at least 90 days prior to the experiments, i.e., at the time of testing, rats were at least 140 days old. Deprived and control male rats used in these experiments were obtained from different litters, that it to say, sibling replication was consistently avoided. At the time of testing, body weights for control and deprived rats were 312 ± 8.7 g and 239 ± 6.1 g, respectively. Animals were maintained at 22 ± 2°C in a 12 L:12 D cycle, lights on at 0700 h with food and water ad lib.

Experimental Design

Experiment 1. In this experiment, effect of CLO on locomotor activity was analyzed in control groups and deprived rats submitted to stress preceded by MOR. The control and experimental conditions were defined by an initial 2 × 2 × 2 × 2 factorial design and the factors under consideration were: nutritional schedule (deprived and control); chronic treatment (no stress and stress); chronic drug administration (SAL and MOR); and drug administration prior to testing (CLO or SAL).

Experiment II. In this experiment we examined CLO-induced hypoactivity when stress was preceded by NAL 5 min before the BETA injection. The conditions were defined by an initial 2 fits 2 fits 4 fits 2 factorial design and the factors under consideration were: nutritional schedule (deprived and control); chronic treatment (no stress and stress); chronic drug administration (SAL, BETA, NAL, and NAL + BETA); and drug administration prior to testing (CLO or SAL).

Chronic Treatment

Adult male rats from both groups (control and deprived) were immobilized for 2 h daily in a Plexiglas restraining device preceded by a SAL (1 ml/kg IP) or MOR (1 mg/kg IP) injection for 7 consecutive days. Animals were restrained between 1000 and 1400 h. Their respective control groups (no stress + SAL or no stress + MOR) received daily SAL or MOR injections for 7 days.

In another set of experiments, the control groups and deprived rats were immobilized according to the same schedule; immobilization was preceded by SAL (1 ml/kg IP), BETA (5 γmg/kg IP), NAL (2 mg/kg IP) 10 min before the onset of restraint or NAL 5 min before the BETA injection. Control groups (saline + no stress, BETA + no stress, NAL + no stress or NAL + BETA + no stress) received daily injections of SAL, BETA, NAL or NAL + BETA for 7 days.

Measurement of Locomotor Activity

Locomotor activity was determined 24 h after the last restraint session and/or injection in every group of animals; it was measured in a square open field (60 × 60 × 60 cm) with 15 × 15 cm square floor markings. Animals were tested 20 min after the SAL (1 ml/kg, IP) or CLO (75 μg/kg, IP) injection between 1000–1600 h under dim white light in a quiet room (19 lx inside the open field). The number of squares entered with all four paws over a period of 10 min was recorded.

Drugs

Morphine-HCl (Lab. Verardo, Buenos Aires, Argentina), Naloxone-HCl (Sigma Chemical Co., St. Louis, MO) and β-endorphin (Sigma Chemical Co.), Clonidine HCl (Catapresan, Boehringer) were dissolved in saline. Injection volume was 0.1 ml/100 g b.wt. for all drugs.

Statistical Analysis

Data were analyzed by means of four-way ANOVA followed by a Fisher's test for post hoc comparisons of groups. The level of statistical significance was set at $p < 0.05$.

RESULTS

Effect of Chronic Immobilization Alone or Associated With Morphine on CLO-Induced Hypoactivity in Control and Deprived Rats

The four-way ANOVA revealed a significant effect of chronic treatment, $F(1, 105) = 7.86$, $p < 0.006$, of drug pretreatment, $F(1, 105) = 156.54$, $p < 0.0000001$, as well as a significant interaction between diet and drug pretreatment, $F(1, 105) = 4.58$, $p < 0.035$, chronic drug administration and drug pretreatment, $F(1, 105) = 4.74$, $p < 0.032$, and between diet, chronic drug administration, and drug pretreatment, $F(1, 105) = 4.23$,

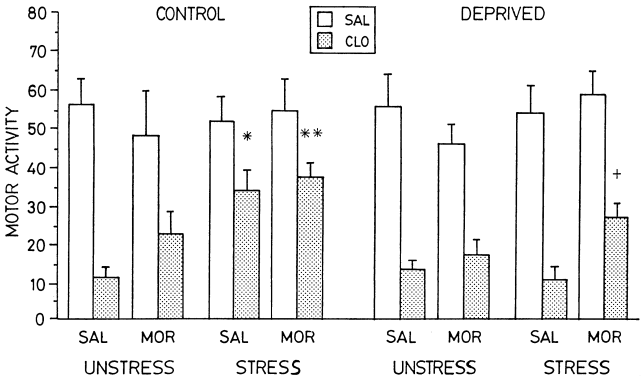

FIG. 1. Effect of chronic stress alone or associated with MOR on CLO-induced hypoactivity in deprived and controls rats. SAL (1 ml/kg, IP) or MOR (1 mg/kg, IP) were injected before each immobilization session. Additional groups of rats were injected daily with SAL or MOR for 7 days. Locomotor activity was measured 24 h after the last immobilization session and/or injections in a square open field. Animals were tested 20 min after CLO (75 figmg/kg IP) or SAL injection. *Different from control unstressed rats treated with SAL $p < 0.05$; **different from control unstressed rats treated with MOR $p < 0.05$; $^{+}$different from deprived stressed rats treated with SAL $p < 0.05$.

$p < 0.042$. Fisher post hoc test ($p < 0.05$), showed that in control unstressed SAL or MOR-treated rats, CLO produced a significant decrease in motor activity when compared with their corresponding control groups. This CLO effect was significantly attenuated in control stressed rats also treated with SAL or MOR. In deprived unstressed SAL or MOR-treated rats, and in deprived stressed rats treated with SAL, CLO produced a significant decrease in motor activity. In deprived stressed MOR-treated rats the effect of CLO on activity was significantly attenuated. Thus, as described in previous works from our lab, chronic immobilization sessions reduced the hypoactivity induced by low doses of CLO in control animals. On the contrary, and as previously described (14), deprived rats did not show this chronic stress-induced attenuation of CLO-induced hypoactivity (Fig. 1). However, in animals subjected to combined MOR and stress treatment, subsensitivity in alpha$_2$-receptors was detected. The administration of seven daily MOR injections in deprived and control rats did not affect the locomotor response to CLO (Fig. 1). It should be stressed that similar levels of motor activity were obtained following SAL or CLO treatment in unstressed control and deprived rats.

Effect of Chronic Immobilization Alone, or Associated With BETA or NAL Treatment, on CLO-Induced Hypoactivity in Control and Deprived Rats

In agreement with the results obtained with MOR for deprived rats, BETA administration prior to each stress session, reinstated the effect of chronic stress on CLO-induced hypoactivity (Fig. 2). The administration of NAL completely abolished the sedative response elicited by CLO in control stressed rats, and in deprived stressed rats treated with BETA. The administration of seven daily BETA injections induced a significant attenuation in CLO-induced hypoactivity in control unstressed animals. Moreover, this effect was blocked by pretreatment with NAL (Fig. 2). It should be noted that in deprived rats, the same schedule of BETA administration did not modify the locomotor response to CLO. The administration of seven daily injections of NAL in deprived and control unstressed rats did not affect locomotor activity scores after CLO administration. The four-way ANOVA (diet × chronic treatment fits chronic drug administration fits drug pretreatment) indicated a significant effect of diet, $F(1, 240) = 5.28$, $p < 0.024$, of chronic treatment, $F(1,240) = 6.58$, $p < 0.011$, of chronic drug administration $F(3,240) = 2.95$, $p < 0.033$, of drug pretreatment, $F(1, 240) = 187.23$, $p < 0.0001$, as well as a significant interaction between diet, chronic treatment, and chronic drug administration, $F(3, 240) = 2.69$, $p < 0.047$, and between diet and drug pretreatment, $F(3,240) = 6.23$, $p < 0.0004$. Fisher post hoc comparisons showed that control unstressed rats treated with SAL, NAL, or NAL + BETA, and deprived unstressed rats treated with SAL, BETA, NAL, or NAL + BETA, displayed a significant decrease in CLO-induced hypoactivity as compared to their corresponding control groups. This CLO effect was abolished in control unstressed rats treated with BETA, in control stressed rats treated with SAL, and in deprived stressed rats treated with BETA. Previous administration of NAL significantly antagonized the attenuation of the CLO-induced hypoactivity in control unstressed rats treated with BETA, control stressed rats treated with SAL, as well as control stressed rats and deprived stressed rats treated with BETA.

DISCUSSION

As previously observed (6), chronic immobilization sessions reduced the hypoactivity provoked by low doses of CLO in control animals. Conversely, and as described (14), the same regime of chronic stress did not attenuate the hypoactivity induced by CLO in undernourished rats, because similar activity responses were obtained in stressed and unstressed undernourished rats.

Much evidence indicates that endogenous opioids are released in response to recurrent stressors, and that these peptides play a modulatory role in the development of adaptive changes on monoaminergic receptors after chronic stress (1,4,6,7). Thus, it has been reported that NAL pretreatment fully antagonized the appearance of adaptive changes on alpha$_2$ and 5-HT$_1$ receptors after chronic stress (6,7). Furthermore, treatment with MOR or BETA and restraint accelerated the onset of these adaptive responses (7). Our present work not only reproduces these previous findings, but also reinforces the view that endogenous opioids play a modulatory role in the development of adaptive changes on monoaminergic receptors after chronic stress, as shown the results obtained from control stressed rats treated with NAL, and from control unstressed rats treated with BETA or NAL fipl BETA. Thus, a combined treatment with NAL and stress completely antagonized alpha$_2$-receptors subsensitivity. In accordance with the hypothesis that opiate receptor stimulation induced changes in monoamine receptors, the 7-day BETA treatment in control unstressed animals elicited adaptive changes in alpha$_2$-receptors, which were blocked when NAL was combined with BETA. Blockade by NAL indicate that the effects induced by BETA are mediated by opiate receptors. However, alteration in alpha$_2$-receptor sensitivity was not observed when MOR was administered for 7 days. The disparate results obtained with the two agonists, MOR and BETA, could be related to pharmacokinetic issues. Thus, although the entrance of sistemically administered BETA into the CNS is limited, and BETA is rapidly inactivated in the brain, BETA from plasma is relatively resistent to enzimatic breakdown and pen-

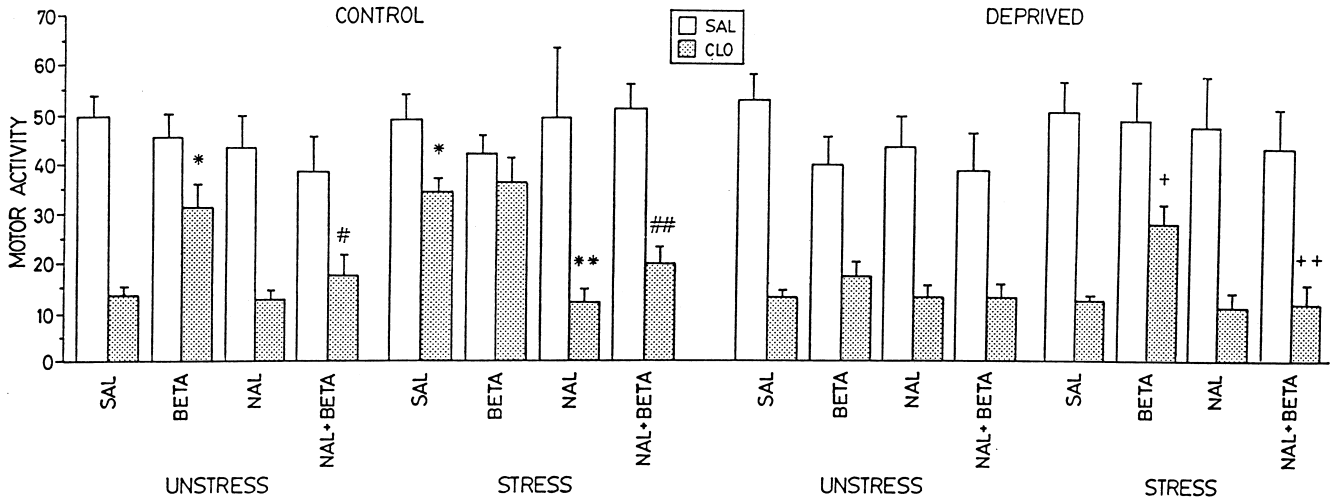

FIG. 2. Effect of chronic immobilization alone, or in conjunction with BETA alone, NAL alone, or NAL 5 min prior to BETA on CLO-induced hypoactivity in control and deprived rats. SAL (1 mL/kg IP), BETA (5 μg/kg IP), NAL (2 mg/kg IP) or NAL + BETA were administered before each immobilization session. Additional groups of rats were injected daily with SAL, BETA, NAL, or NAL + BETA for 7 days. Locomotor activity was measured 24 h after the last immobilization session and/or injection in a square open field. Animals were tested 20 min after CLO or SAL injection. *Different from control unstressed rats treated with SAL $p < 0.05$; #different from control unstressed rats treated with BETA $p < 0.05$; **different from control stressed rats treated with SAL $p < 0.05$; ##different from control stressed rats treated with BETA $p < 0.05$; $^{+}$different from deprived stressed rats treated with SAL $p < 0.05$; $^{++}$different from deprived stressed rats treated with BETA $p < 0.05$.

etrates rather slowly into CSF (11,23). So, during chronic administration of systemic BETA, the persistent activation of a specific population of opiate receptors mediating the development of adaptive changes in alpha$_2$ receptors could occur. Furthermore, in a previous work from our lab, 3-day treatment with BETA and MOR at the same range of doses as in the present work showed that BETA induced a trend towards increasing behavioral reactivity in 5-HT$_1$ sites, while MOR did not (7). In summary, the results obtained from control stressed rats treated with NAL and from control unstressed rats treated with BETA or NAL fipl BETA, strongly confirm former findings suggesting that endogenous opioids play a modulatory role in the development of adaptive changes on monoaminergic receptors after chronic stress (4,6,7)

With regard to malnourished animals, a combined treatment with stress, and either MOR or BETA, elicited changes in sensitivity to CLO. NAL pretreatment abolished the BETA-induced effects. Contrary to what was observed in unstressed control rats, the 7-day BETA treatment did not modify CLO-influence locomotor activity. This could be explained by the fact that these animals display subsensitivity in their brain opiate receptors, due to lower density or affinity. Further, other authors have reported that adult rats undernourished at early life display diminished endorphin release following shock or novel training procedures (21,22,31). Therefore, it could be argued that these animals may present both modifications in their opiate receptors and decreased BETA release when facing stressful situations. Even though further investigation is necessary to clarify this topic, it is important to note that the combined treatment with stress and MOR or BETA in undernourished rats induced subsensitivity in alpha$_2$-receptors, and that NAL pretreatment abolishes the BETA-induced effects. These results expand previous findings that indicate that combined treatment with stress and MOR in undernourished animals induced adaptive changes in serotonergic sites (15), an effect that is blocked by NAL. Taking into account this evidence along with the present findings, it could be suggested that perinatal undernutrition impairs the activation of an opiate mechanism involved in the development of changes in adaptation to stress.

Findings from different behavioral paradigms, such as an exaggerated behavioral response to stress, have been consistently noticed in rats submitted to perinatal malnutrition (9,17,24), suggesting that this insult during early life affects the ability to cope with the environmental demands at adult age. At present, there is growing evidence that adaptive changes in monoaminergic receptors are linked to the stress adaptation process. Recently, we have shown that adult rats submitted to a protein deprivation schedule at perinatal age, failed to develop subsensitivity of presynaptic dopaminergic and alpha$_2$-adrenoceptors (14), as confirmed in the present work, as well as supersensitivity of 5-HT$_1$ receptors after repeated stress (15). Hence, this evidence has led us to postulate that the behavioral alterations observed when malnourished animals are confronted with highly stressful situations may be, at least in part, a consequence of failure to develop adaptive changes to stress. Moreover, the results obtained in the present work as well as previous finding (i.e., that the combination of MOR or BETA and stress reinstates these monoaminergic changes) may strongly indicate that the deficit observed in malnourished rats might be related to a functional deficiency in the stress-induced activation of an endogenous opiate process.

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