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BRIEF COMMUNICATION

Reduced Anti-Immobility Effect of Repeated Desipramine (DMI) Treatment in Adult Rats Undernourished at Perinatal Age[1]

V. A. MOLINA, E. A. KELLER AND O. A. ORSINGHER

Departamento de Farmacología, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba Sucursal 16, C.C. 61, Cordoba, Argentina

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MOLINA, V. A., E. A. KELLER AND O. A. ORSINGHER. *Reduced anti-immobility effect of repeated desipramine (DMI) treatment in adult rats undernourished at perinatal age.* PHARMACOL BIOCHEM BEHAV 26(2) 417–419, 1987.—Adult rats submitted to a protein deprivation schedule at perinatal age showed a reduced anti-immobility effect following seven days of DMI treatment (20 mg/kg/day) in the forced swimming test. The ineffectiveness of DMI treatment is attributed to the inability of deprived animals to produce neuronal adaptative changes in central monoaminergic pathways.

Perinatal undernutrition DMI Behavioral despair test

A large body of evidence demonstrates the deleterious effects of perinatal undernutrition on anatomical, neurological, neurochemical and behavioral parameters [10]. Among those effects the understanding of alterations in different aspects of the metabolism of neurotransmitters of the CNS may be relevant in order to clarify pathophysiological aspects of the disturbances induced by early undernutrition, as well as the functional meaning of such changes.

As regards the serotonergic system, a marked subsensitivity to 5-HT agonists in adult rats deprived both at pre and postnatal age has been reported [6]. On the catecholaminergic system, rats submitted to a protein deprivation schedule similar to that used in this experiment showed an increased turnover rate of DA and NA in whole brain, together with an enhanced tyrosine-hydroxylase activity, which suggests an increased neuronal activity [9]. This fact induces a significant reduction in the number of alpha and beta adrenergic binding sites [7].

On the other hand, it is widely accepted that a chronic treatment with antidepressant agents is associated with adaptative changes in central monoaminergic receptors [1,16]. Since early undernutrition produces a persistent change in brain adrenergic receptors, it seemed interesting to study the functional effects induced by a repeated treatment with DMI on the forced swimming test, considered an animal model of experimental depression [11].

METHOD

Animals

A protein deprivation schedule as previously described was used [5] Pregnant female rats (Wistar strain) were divided into two groups at 14 days pregnancy, housed in individual Plexiglas cages and fed isocaloric diets containing a 24% and 8% casein (control and deprived, respectively). After weaning (24 days), pups continued consuming the same diets as their dams until they reached 50 days of age. Thereafter, both groups were given balanced standard chow for at least 90 days before being used, i.e., experiments were performed with rats at least 140 days old. Animals were maintained at 22±2°C in a 12 hr-12 hr light-dark cycle. Food and water were available ad lib.

Measurement of Immobility

Male rats from both groups (control and deprived) were individually forced to swim in a vertical Plexiglas cylinder (height: 40 cm; diameter: 18 cm) containing water at 25°C

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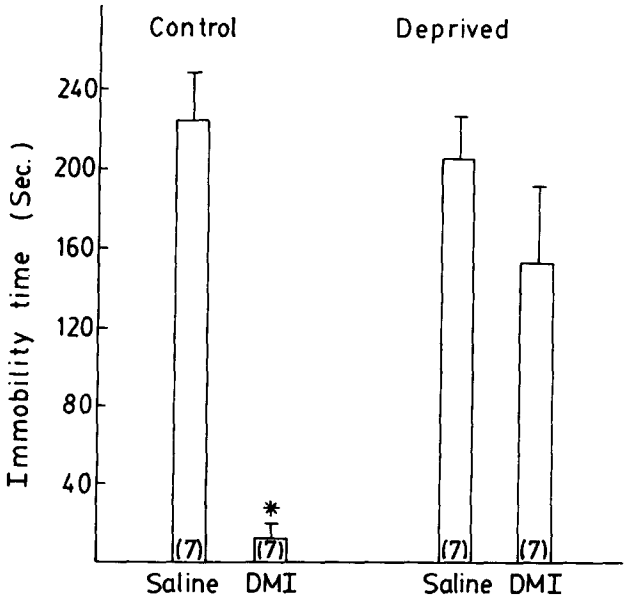

FIG. 1. Effect of 7-days DMI treatment (20 mg/kg/day) on the immobility time in control and perinatal undernourished rats during a 5 min period. Means values±SEM. Statistical differences were carried out by two-way ANOVA. Subsequent *t*-test indicated that control DMI treated group was significantly lower than the remaining scores of the other three groups ($*p<0.01$).

with a depth of 17 cm [11]. After 15 min they were removed to a heated chamber at 32°C and allowed to dry for 30 min.

For drug testing, a schedule of treatment according to Borsini *et al.* was employed [2]. Control and deprived rats were treated with DMI, hydrochloride (20 mg/kg/day IP) or with saline (1 ml/kg) during 7 days, and total immobility time was measured during a 5 min period. A rat was considered to be immobile whenever it remained floating passively in the water, in an upright position, making only small movements to maintain its head just above the surface. The first dose of DMI was injected immediately after the 30 min drying period; the last one 1 hr before test.

RESULTS

As previously described, a 7 day treatment with DMI reduced the immobility time of control animals in the forced swimming test. On the contrary, perinatally deprived rats showed no anti-immobility effect following the same repeated administration of DMI (Fig. 1). It is important to point out that no difference in immobility was observed between control and deprived rats without antidepressant treatment.

DISCUSSION

Our data demonstrate that adult rats, submitted to a protein deprivation at perinatal age and then recovered with balanced chow, showed a lack of effect to a prolonged DMI treatment in the forced swimming test.

Long term administration of antidepressant drugs induces several adaptative changes in the central monoaminergic system of experimental animals. As regards the catecholaminergic system, different reports indicate that changes in noradrenergic and/or dopaminergic function may be involved in the mechanism of action of antidepressant drugs. The most consistently reported findings are the reduction in beta-adrenergic sensitivity and/or density, i.e., beta-receptor down regulation and reduced accumulation of cAMP induced by NA [16]. In addition, a reduction in the sensitivity of presynaptic receptors, both alpha-2 and dopaminergic, has been also reported [4, 12, 13, 14]. Although the functional significance of these receptor changes remains unclear, it has been suggested that the anti-immobility effect following a repeated treatment with antidepressants is induced by an enhancement of dopaminergic activity [2]. On the other hand, experiments performed to investigate if a single injection of DMI was able to antagonize the depressive effects of reserpine [15] showed that DMI (20 mg/kg) counteracts in both control and deprived rats the depressive syndrome induced by 9 mg/kg of reserpine (data not shown). This result suggests that the reuptake sites on which DMI acts is not affected by early undernutrition. Thus, we may tentatively conclude that undernourished rats are less capable than controls in producing adaptative changes in the central neuronal pathways that may account for the decreased effect observed after DMI administration. Notwithstanding, taking into consideration that early undernutrition induces a permanent activation of the central catecholaminergic system [9] that affects the density of adrenergic receptors [7], alternative explanations cannot be ruled out. Further investigations are desirable in order to clarify the mechanism involved in the lack of effect of DMI.

This report extends previous findings that demonstrate an altered reactivity to different pharmacological treatments in adult rats which were deprived at early life, both at peripheral and central levels, such as subsensitivity to adrenergic agonists on the vascular bed [5] and other sympathetic innervated organs [8], lower reactivity to central effects of 5-HT agonists [6] and increased response after a repeated amphetamine treatment [3]. If gross extrapolation to the clinic may be considered, these experimental data suggest the possibility of an altered reactivity to therapeutic treatments in subjects malnourished at early life.

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