Pharmacology Biochemistry & Behavior, Vol. 21, pp. 181–184, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Inhibition of Isolation-Induced Changes in Aminergic Transmission by Chronic Lithium Treatment

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Received 28 June 1983

OEHLER, J., M. JÄHKEL AND J. SCHMIDT. *Inhibition of isolation-induced changes in aminergic transmission by chronic lithium treatment.* PHARMACOL BIOCHEM BEHAV 21(2) 181–184, 1984.—Social isolation of mice leads to changes in aminergic transmission systems. After 6 weeks of isolation, an increase of apomorphine-stimulated climbing behavior is seen, reflecting an isolation-induced dopaminergic supersensitivity. After 1–3 weeks of isolation, a decrease of clonidine sedation is detectable, suggesting the development of noradrenergic α_2-receptor subsensitivity. The isolation-induced changes of both drug effects are prevented by lithium given over the time of isolation.

Social isolation Aminergic changes Apomorphine Clonidine Prevention by lithium

SOCIAL isolation induces changes in the behavior of rodents that have been defined by Hatch *et al.* [7] and Valzelli [17] as the "isolation syndrome." Such changes are related to plastic events in the CNS. It is known from neurochemical [15,16], microiontophoretic [1,11] and behavioral [16] studies that social isolation results in sensitivity changes in cerebral aminergic transmission systems.

In previous studies using the microiontophoretic application of transmitter substances to striatal neurons of rats, we have found isolation-induced sensitivity changes reflecting supersensitivity of the dopaminergic system [11]. Recently, isolation-induced changes in aminergic receptor binding sites were demonstrated by Guisado *et al.* [6] and Kraeuchi *et al.* [8].

We pursued a further elucidation of the isolation syndrome by carrying out several behavioral experiments. The climbing behavior of mice is known to be a suitable pharmacological model for characterization of aminergic transmission processes [14]. Therefore, the following study was designed to describe isolation-induced sensitivity changes in the dopaminergic and adrenergic system using the climbing behavior of mice affected by apomorphine and clonidine, respectively.

The influence of drug treatment on isolation-induced alterations, especially the ability of substances to reverse or to prevent such alterations remains to be investigated. Some results demonstrate that this animal model may be valuable for the discovery of antidepressant drugs, regardless of their mechanism of action [5].

Lithium is one of the most interesting clinically used substances for prevention of manic episodes in mono- and bipolar affective disorders. Pert *et al.* [13] suggested that lithium may act in affective disorders by stabilizing receptor sensitivity. In this connection, the question arises whether lithium is able to prevent isolation-induced changes in aminergic transmission processes.

METHOD

Male albino mice (strain AB) 5–6 weeks old, supplied with food and water ad lib, were kept individually in cages (10×10×25 cm) for 3 or 6 weeks. The isolated animals could not see each other. Control animals lived in groups of 20 in larger plastic cages (50×30×10 cm). All animals were kept in rooms maintained at standard laboratory conditions. The handling of the isolated and group-housed animals was restricted to cleaning the cages (once a week). One group of isolated and one of group-housed mice received about 4 mmol/kg/day lithium (LiCl) in the drinking water. The blood level of lithium was 0.8 mmol/l. The lithium level has been photometrically determined after three weeks of lithium treatment by the method of DAB [2]. The measurements were carried out between 8–10 a.m. This lithium treatment did not affect the weight of the animals compared with the controls. At higher concentrations of lithium, we have observed weight reduction and changes in behavior.

Climbing experiments were carried out according to the method of Protais *et al.* [14]. Animals were put separately into special cylindric cages of copper screen wire (12 cm in diameter and 20 cm in height). After 30 minutes habituation time, we registered the stereotype climbing behavior of mice for 5 minutes. The animals were scored individually five times at the beginning of each minute in the following manner: 0—mouse with all paws on the floor, 1—mouse with its forepaws on the climbing wall, 2—mouse with all paws on the climbing wall. The values of each mouse and of all mice in one group (commonly 10) were averaged. After the registration of the baseline climbing scores, animals received drug administrations.

For studying dopaminergic sensitivity changes, apomorphine was administered intraperitoneally in a cumulative manner every 15 minutes. The doses used were: 0.05, 0.1,

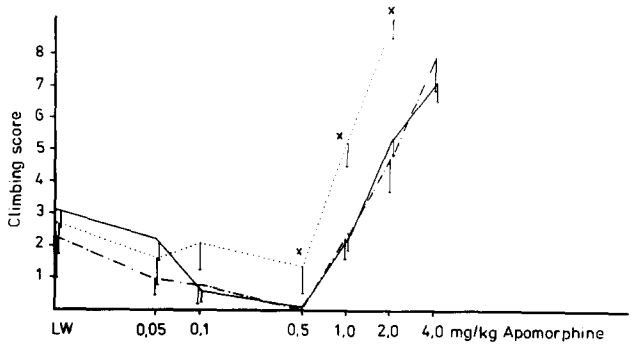

FIG. 1. Climbing behaviour in mice: Dose-response curve of apomorphine given in a cumulative manner, ——— group housed mice (n=10) . . . social isolated mice (n=10, 6 weeks), —·—·— social isolated mice treated with lithium (n=10, 6 weeks). Means± S.E.M. $^{x}p=0.01$.

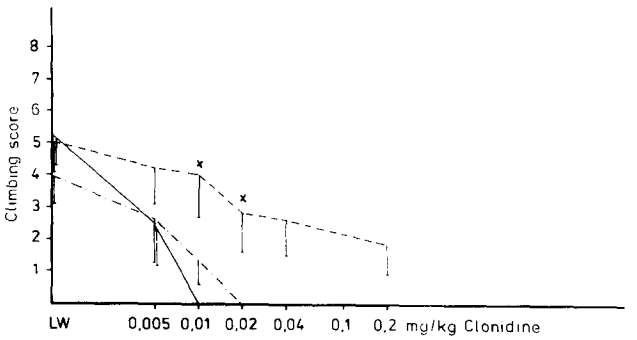

FIG. 2. Climbing behaviour in mice: Dose-response curve of clonidine given in a cumulative manner, —— group housed mice, — — —social isolated mice (n=10, 3 weeks), —·—·— social isolated mice treated with lithium (n=9, 3 weeks). Means±S.E.M. $^{x}p=0.01$.

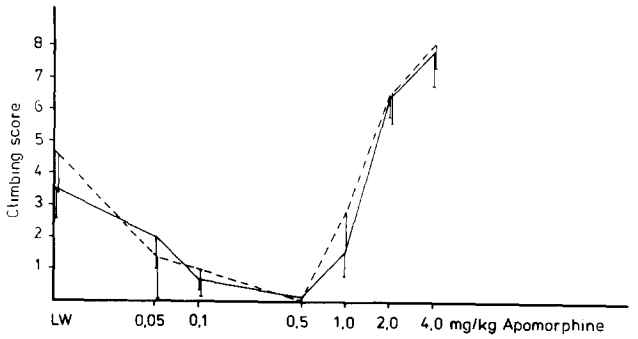

FIG. 3. Climbing behaviour in mice: Dose-response curve of apomorphine given in a cumulative manner, — — — group housed mice (n=10), —·—·— group housed mice treated with lithium (10 weeks). Means±S.E.M. (n=10), no statistical differences (all p-values>0.05).

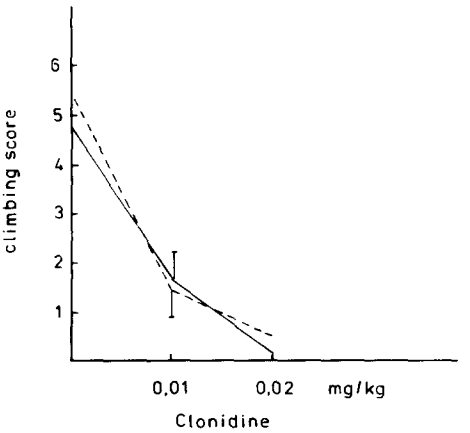

FIG. 4. Climbing behaviour in mice: Dose-response curve of clonidine given in a cumulative manner in ——— group housed mice (n=10), — — — group housed mice treated with lithium (n=10, 4 weeks), no statistical differences (all p-values>0.05).

0.5, 1.0, 2.0 and 4.0 mg/kg. Clonidine was given also cumulatively every 15 minutes in the following doses: 0.005, 0.01, 0.02, 0.04, 0.1 and 0.2 mg/kg. In order to obtain a gradual evaluation, the animals were scored five times at the beginning of each minute, starting 10 minutes after the administration of each dose. Except for the administration of drugs, the animals were kept in the climbing cages until the end of the experiments.

Comparisons between controls and isolates, as well as between drug treatments were statistically evaluated with the Students t-test.

RESULTS

Apomorphine given in cumulative doses affects the climbing behavior of mice in a biphasic manner. Lower doses (up to 0.5 mg/kg) decreases the climbing behavior of controls. The higher doses of apomorphine facilitate the climbing behaviour (Fig. 1).

After prolonged isolation (6 weeks), mice show signs of postsynaptic dopaminergic supersensitivity. Stimulatory effects of higher apomorphine doses are considerably more pronounced, whereas only a small decrease of spontaneous climbing can be induced by lower doses of apomorphine. This reflects a tendency of presynaptic dopaminergic subsensitivity (Fig. 1).

Cumulatively administered clonidine causes a dose dependent inhibition of climbing behavior in group-housed control mice. The highest dose leads to a complete inhibition of the stereotype climbing behavior (Fig. 2). Following short-term isolation of mice (1–3 weeks), the sedative effect of clonidine is significantly reduced, reflecting a subsensitivity of the investigated adrenergic system (Fig. 2). These sensitivity changes, which appear to be dependent on isolation, have never be seen before (Fig. 1). Lithium given in drinking water during the period of isolation is able to completely prevent the isolation-induced sensitivity changes in both the dopaminergic apomorphine and the noradrenergic clonidine tests.

Lower and higher doses of apomorphine have the same effects on mice receiving lithium during a 6-week isolation period as on group-housed control mice.

Mice isolated for 3 weeks and supplied simultaneously with lithium in the drinking water show no changes of

clonidine sedation and react in the same manner as group-housed controls (Fig. 2).

Group-housed controls receiving lithium in the drinking water for some weeks develop no alterations in the climbing behavior affected by apomorphine (Fig. 3) and clonidine (Fig. 4) when compared with group-housed mice drinking pure water.

DISCUSSION

Isolation-induced sensitivity changes have been demonstrated in the aminergic transmission system by several investigators using neurochemical [15,16], electrophysiological [1,11] and behavioural-physiological [12,15] methods. Recognizing that climbing behavior is a sensitive model for the characterization of aminergic, especially dopaminergic transmission processes, we wondered whether isolation-induced sensitivity changes are also evident in the climbing behavior of mice.

Our climbing experiments show marked changes in sensitivity to apomorphine and clonidine and support the hypothesis regarding isolation-induced changes in dopaminergic and noradrenergic transmission systems.

Our earlier studies [10] of the enhanced sensitivity of striatal neurons to dopamine as well as the enhanced number of dopaminergic binding sites reported by Guisado *et al.* [5] together with the present results support an isolation-induced development of postsynaptic dopaminergic supersensitivity. In their investigations with flupentixol, Leonard and Morinan [9] likewise proposed an altered receptor sensitivity in the striatum after social isolation.

Several isolation-related changes in the noradrenergic system are described. Kraeuchi *et al.* [8] are able to show a tendency toward decreased β-receptor binding sites and a decreased adenylatcyclase sensitivity, which are interpreted as signs of diminished noradrenergic transmission. On the other hand, an enhanced noradrenergic sensitivity had been found by Welch and Welch [19]. This increase in noradrenergic sensitivity is confirmed in several studies. Speiser and Weinstock [15,18] demonstrate it using isoprenaline and propranolol. Recently Frances *et al.* [3] showed the enhanced noradrenergic sensitivity in apomorphine-induced hypothermia affected by salbutamol. Whereas all these experiments suggest a postsynaptic noradrenergic supersensitivity, our results demonstrate the development of a decreased clonidine sedation in isolated mice reflecting the development of an α_2-adrenergic receptor subsensitivity.

One of the most fascinating substances in the treatment of affective disorders is lithium. In binding studies, Pert *et al.* [12] demonstrate the ability of lithium to antagonize supersensitivity evoked by chronic haloperidol administration. The same authors verify the prevention of haloperidol-induced sensitivity changes by chronic lithium administration in electrophysiological experiments on dopaminergic neurons. On the basis of these experimental data, they conclude that lithium may act clinically in affective disorders by stabilizing receptor sensitivity. Some results described recently show the ability of lithium to stop the haloperidol-induced supersensitivity of pre- and postsynaptic dopamine receptors in the rat brain [4]. The absence of enhanced apomorphine stimulation in the group of isolated mice treated with lithium proves that the development of isolation-induced changes in dopaminergic sensitivity can also be prevented by lithium. In addition, the results demonstrate that the isolation induced effects in clonidine sedation are abolished in animals receiving lithium during the isolation period. We wonder whether the lithium effect is directly related to the adrenergic system. On the one hand, the investigations of Frances *et al.* [3] assume lithium to be ineffective in a noradrenergic binding study. They show that β-adrenergic receptor binding sites do not undergo alterations by lithium treatment during isolation. On the other hand, it has been reported that isolation-induced supersensitivity of the noradrenergic system is blocked by lithium as shown in the locomotor activity influenced by salbutamol [3]. Using specific low doses of clonidine, we demonstrate the ability of lithium to prevent isolation-induced changes in the presynaptic α_2-receptor population of the noradrenergic system.

Our study, together with others, demonstrate that social isolation of mice causes adaptive changes in aminergic transmission systems. Therefore we suggest that the development of plastic changes in aminergic systems represents a basic neurobiological mechanism of the isolation syndrome in animals. The ability of lithium to prevent the development of aminergic sensitivity changes, described in our experiments, is remarkable. Whether lithium's ability to block isolation-induced sensitivity changes is general or specific, and the problem of the functional importance of the lithium effects must be cleared up in future.

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