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BRIEF COMMUNICATION

On the Role of Serotonin in Apomorphine-Induced Locomotor Stimulation in Rats

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GRABOWSKA, M. AND J. MICHALUK. *On the role of serotonin in apomorphine-induced locomotor stimulation in rats.* PHARMAC. BIOCHEM. BEHAV. 2(2) 263–266, 1974. – The locomotor activity of rats injected with apomorphine (1.0 or 5.0 mg/kg) was measured. The increase of locomotion caused by apomorphine was stronger in rats pretreated with BOL or methysergide and in some case with p-chloroamphetamine. LSD did not change the stimulation evoked by apomorphine or decreased it. The results are discussed according to the previously expressed suggestion about the possible inhibitory role of serotonin in apomorphine-induced locomotor stimulation in rats.

Apomorphine Locomotor activity Serotoninolytics p-Chloroamphetamine

APOMORPHINE, a central dopamine receptor stimulating agent, transiently increases the locomotor activity of rats [15,24] and the subsequent decline of hyperactivity is inversely related to the elevation of the serotonin metabolite, 5-hydroxyindoleacetic acid concentration in the brain [15]. It seems likely that apomorphine activates central serotonin neurons, and owing to that, attenuation of its stimulatory effect on locomotor activity can appear. As the mentioned apomorphine effects are abolished by pretreatment with butyrophenones [15,24] it seems that apomorphine acts on serotonin neurons indirectly, by stimulation of dopamine receptor.

To find further data confirming the possible role of serotonin as a moderator of apomorphine-induced locomotor stimulation we investigated the influence of several drugs affecting brain serotoninergic system on the locomotor stimulation evoked by apomorphine in rats.

METHOD

The experiments were carried out on male Wistar rats, weighing 160–240 g.

The rats tested for locomotor activity were placed singly for 45 min in a photocell (two crossed light beams) actometer (with dimensions 40 × 40 × 21 cm), injected with saline (s.c.) and 45 min later with apomorphine (1.0 or 5.0 mg/kg s.c.) and were immediately returned to the actometer. The locomotor activity was recorded every 15 min for 2 hr after the second injection. The scheme of the experiments is presented in Fig. 1. Each group consisted of 10 animals. For statistical evaluation (Wilcoxon two sample test) [31] the comparison of values obtained in experimental group and the control group, treated with apomorphine only, was done at 15 min interval each.

Apomorphine hydrochloride (McFarlane), BOL-148 (Sandoz), methysergide hydrogenmaleate (Sandoz), LSD-25 (Delysid, Sandoz) and d,l-p-chloroamphetamine hydrochloride (Ferrosan) were injected as physiological saline solutions or suspensions with 3% tween 80 in a volume of 4.0 ml/kg.

RESULTS

Apomorphine at doses 1.0 and 5.0 mg/kg increased the motor activity of rats. The applied photocell method recorded mainly running and coordinated gross movements, omitting the small ones, connected with stereotyped sniffing and gnawing caused by apomorphine in rats. The motor stimulation evoked by apomorphine lasted usually up to 45 min, then declined (see Fig. 1). The maximal stimulatory effect could be seen 30 min after apomorphine administration, irrespective of the dose used.

Pretreatment with BOL or methysergide, at the doses of 2.0 and 1.0 mg/kg respectively, did not affect the spontaneous locomotor activity of rats, but significantly potentiated the stimulatory effect of both doses of apomorphine (see Fig. 2).

LSD (1.0 mg/kg i.p.) injected immediately before time 0 neither changed spontaneous locomotor stimulation (see Fig. 2); only at the first 15 min interval after apomorphine (1.0 and 5.0 mg/kg) administration, the increase of the stimulatory effect of the latter was evident. LSD given

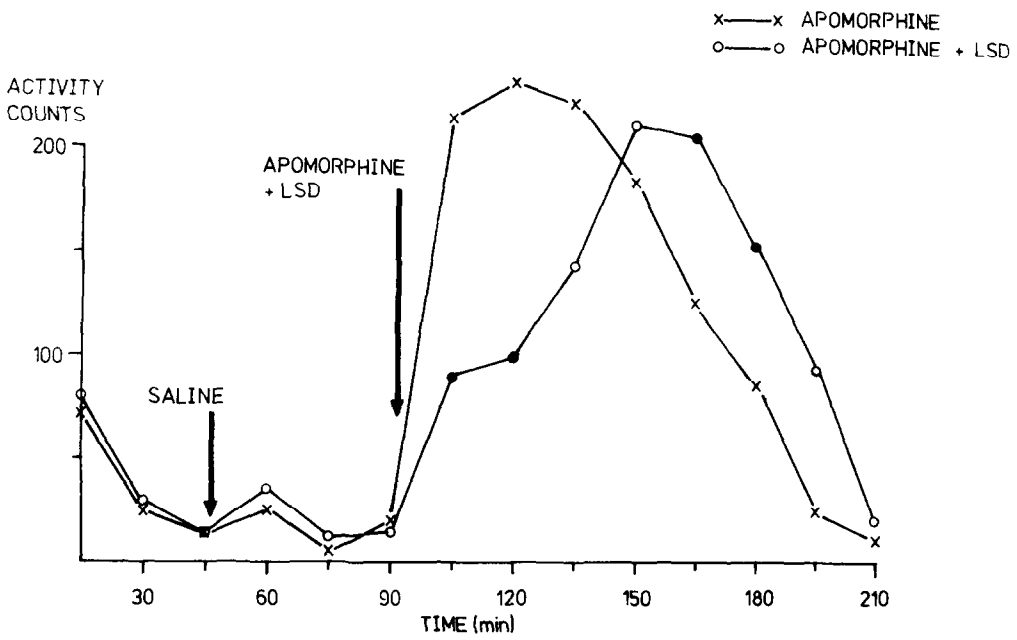

FIG. 1. The influence of LSD (1.0 mg/kg s.c.) on the locomotor stimulation evoked by apomorphine (5.0 mg/kg s.c.) in rats. Black circles indicate the results statistically significant comparing with control group. For further explanations see METHOD.

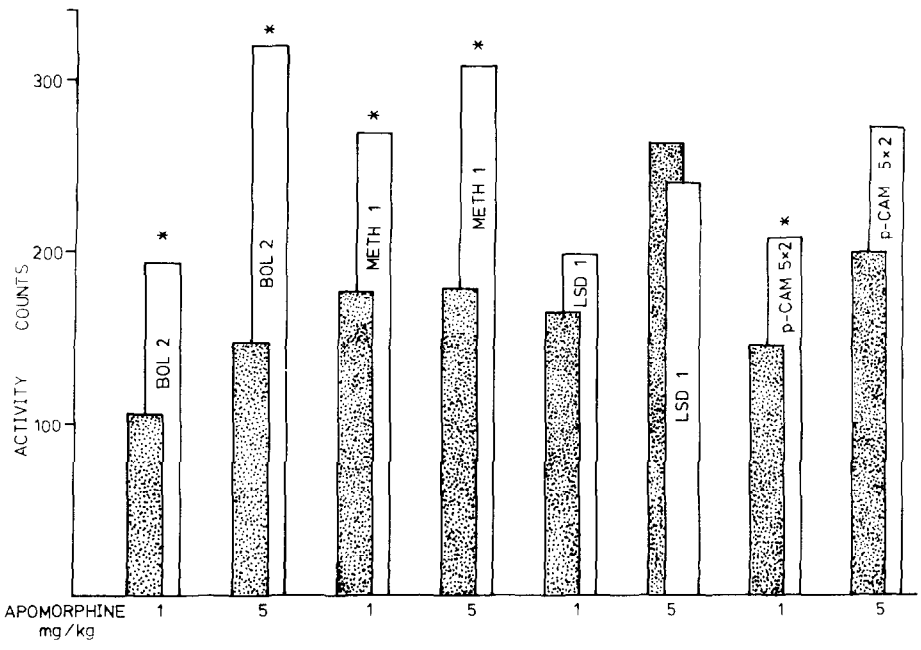

FIG. 2. The influence of BOL, methysergide (METH), LSD and p-chloroamphetamine (p-CAM) on the apomorphine-induced locomotor stimulation in rats. The results are expressed as mean values calculated from four determinations performed in 15 min interval after apomorphine injection. The statistical significance was signed by asterisk if at least 2 out of 4 values compared were statistically significant.

30 min before apomorphine application did not influence the stimulation of locomotor activity induced by apomorphine. The stimulatory effect of apomorphine was significantly diminished when LSD was administered 15 min earlier or simultaneously with apomorphine. After combined treatment with LSD and higher dose of apomorphine the curve of locomotor stimulation was shifted by about 30 min compared with the value obtained in the group treated with apomorphine only (see Fig. 1). In the course of above mentioned experiments the potentiation of apomorphine-induced stereotypy could be observed, especially when LSD was injected shortly before apomorphine administration.

p-Chloroamphetamine (10.0 mg/kg, 17 hours before the test), in different experiments caused decrease as well as increase of spontaneous locomotor activity in rats. At the same time, the locomotor stimulation caused by apomorphine was not influenced by p-chloroamphetamine. The latter, injected subchronicaly, during 5 days (2.0 mg/kg daily) did not affect the locomotion of rats, measured three days after the last dose, but it intensified the stimulation caused by apomorphine (see Fig. 2). The result however, was statistically significant only in case of lower dose of apomorphine.

DISCUSSION

Serotonin seems to play a inhibitory role in different forms of behaviour [11, 14, 22, 33, 34, 35] including the motor activity [3, 7, 20, 23].

As it was mentioned in the introduction our earlier experiments [15,16] inclined us to the assumption that serotonin can be responsible for quick extinction of locomotor stimulation brought about by apomorphine in rats. The stimulatory effect of apomorphine was stronger in rats depleted of brain serotonin by inhibition of tryptophan hydroxylase activity [15] or by destruction of midbrain raphe area (unpublished data), while it was weaker in 5-HTP-pretreated animals [15]. It should be mentioned however, that the method of evaluation of locomotor activity was different from described here. The similar, stimulatory effect of apomorphine, observed in case of shortly measured, exploratory activity [15,24] and the cumulative activity estimated here, let us believe that the results can be compared.

The potentation of amphetamine-induced locomotor stimulation in rats by lesion of midbrain raphe area and by inhibition of synthesis of brain serotonin were described recently by others [23,28].

Part of presented results seems to corroborate our hypothesis. BOL and methysergide, drugs regarded as serotoninolytics [2, 4, 5, 6, 9], caused potentation of the locomotor stimulation brought about by apomorphine.

LSD, however, which was described as drug blocking serotoninergic receptor [2, 4, 6] as well as stabilizing intraneuronal serotonin [8, 18, 21, 30] did not increase the apomorphine-induced locomotor stimulation. The result obtained is rather surprising as we have found previously that LSD was able to counteract the elevation of brain 5-hydroxyindoleacetic acid concentration caused by apomorphine [17]. The changes in brain serotonin and its metabolite induced by L-DOPA were attenuated by LSD too [25]. It seems, that the lack of effect of LSD and its ability even to decrease the apomorphine-induced locomotor stimulation derives from the potentiation by the drug of the apomorphine-induced stereotypy. LSD, which can induce stereotypy alone [12,29], intensified the action of apomorphine to the extent limiting the big movements and running, registered mainly in our method. The possibility of stimulation of serotonin receptor, suggested for LSD [1] should be also considered. p-Chloroamphetamine, drug lowering concentration of brain serotonin [10, 13, 19, 26, 27, 32] increased apomorphine-induced locomotor stimulation only in some experiments. Other factors than inhibition of tryptophan hydroxylase activity by the drug should be taken into account. p-Chloroamphetamine can release serotonin or inhibit its reuptake [19,36]. It is worth to mention that in our experiments, the increase of the action of apomorphine could be seen after chronic administration of p-chloroamphetamine, three days after the last injection. It seems very likely that under those conditions the only effect of the drug was the remote result of its action, namely the decrease of brain serotonin.

The presented results seem to confirm our hypothesis about the possible inhibitory role of serotonin in the apomorphine-induced locomotor stimulation in rats.

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