GABA-ERGIC MODULATION OF RECOVERY OF MEMORY TRACE RECALL, IMPAIRED BY AMNESIA, BY ACTIVATION OF THE DOPAMINERGIC SYSTEM

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Experimentally induced amnesias can be weakened by pharmacological agents differing in their neurochemical spectrum of action, and modifying the functional state of one or more mediator systems of the brain, whose importance in the development of different kinds of amnesia is confirmed by an adequate volume of evidence [1, 2, 4, 10, 11]. It is quite evident that improvement of memory under the influence of every neuropharmacological agent is accompanied by coordinated changes in the activity of many neurochemical systems of the brain. In mechanisms responsible for this coordination of changes during memory trace recall, dopaminergic (DA-ergic) and GABA-ergic systems may participate. Interaction between these systems in extrapyramidol and limbic DA-projection pathways has been demonstrated by biochemical, pharmacological, and electrophysiological studies [6, 8, 13]. Dynamic equilibrium between DA and GABA in the basal ganglia and limbic system differs significantly in psychoneurotic states such as Parkinson's disease, Huntington's chorea, depression, dyskinesia, and certain forms of schizophrenia [6, 9, 13]. Although relations between DA and GABA in motor functions have been actively analyzed in the world literature, virtually no investigations of this kind have been conducted on recall of disturbed memory traces. This paper describes an attempt to discover the characteristics of weakening of amnesia through intervention on the DA-system after activation of GABA- and benzodiazepine (BD) receptors (a neurochemical set).

EXPERIMENTAL METHOD

Experiments were carried out on 219 male BALB/c mice weighing 20-22 g. A conditioned passive avoidance reflex (CPAR) was formed in the animals by the usual method in an experimental chamber with two compartments — one light (safe) and the other dark (dangerous). For 24 h before training the mice were at lowed to become familiar with the situation for 180 sec. On the day of training, on moving into the dark compartment the animal received a painful electrical stimulus of the skin with a strength of 1 mA, lasting 2 sec.

Anemia was induced by placing the animal immediately afterelectric shock in the dangerous compartment for 5 min [12]. All the animals were divided into four series (A-D), which differed from one another in the neurochemical set: A) training and amnesia unaccompanied by changes in functional state, B) 30 min before training and induction of amnesia, the animals received an injection of the BD-receptor activator diazepam ("Gedeon Richter," Hungary) in a dose of 1 mg/kg, C) injection of the $GABA_B$-receptor activator muscimol ("Serva," West Germany) in a dose of 0.5 mg/kg. The presence of CPAR and amnesia was tested 24 h after training. Mice of each series were divided into four groups. On the 2nd day, 30 min before testing, the drugs were injected: group 1 in each series received physiological saline, group 2 received the dopamine reuptake blocker bupropion ("Burroughs Wellcome," USA) in a dose of 30 mg/kg, group 3 received (+)-3-PPP ("Astra Pharmaceuticals," Sweden) in a dose of 10 mg/kg, activating postsynaptic DA-receptors, and group 4 received the quinpyrole-selective D-2-receptor agonist Ly-141555 ("Eli Lilley," USA) in a dose of 1 mg/kg. All drugs were given in a volume of 0.2 ml per mouse.

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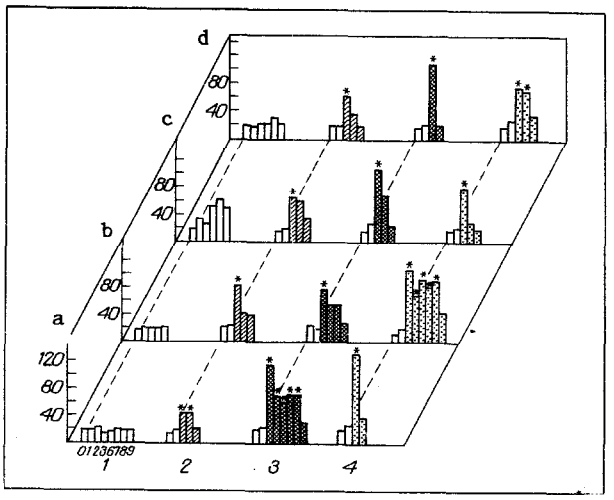

Fig. 1. Effects of activation of dopaminergic system on recovery of memory trace recall in amnesic mice after preliminary injection of receptor agonists of the GABA-ergic system. Abscissa, time of testing (in days); ordinate, LP of passage (in sec). $*p < 0.05$ compared with corresponding groups receiving physiological saline.

Each group consisted of at least 10 mice. The latent period (LP) of passage from the light into the dark compartment was recorded. The significance of differences between parameters after inject ion of the drugs, compared with injection of physiological saline, was assessed by Student's t test.

EXPERIMENTAL RESULTS

The results are given in Fig. 1. It will first be noted that all the animals developed deep amnesia after a combination of training with the amnesia-inducing agent, which could be recorded after 24 h. Injection of physiological saline on the 2nd day before testing did not change LP of passage in any of the series (Fig. 1, a-d, 1).

Bupropion caused a small but statistically significant increase in LP of passage in mice whose amnesia was formed without any change in the functional state of the GABA-system (Fig. 1a, 2). If, however, amnesia developed against the background of activation of BD-receptors by diazepam, a significant increase was observed compared with A2 in the effectiveness of bupropion in improving recall of CPAR (Fig. 1b, 2). Whereas in group A2 the mean value of LP of passage after bupropion was 44 ± 10 sec, in group B2 it was 85 ± 19 sec (the numbers indicate the mean value and error of the mean, $M \pm m$). Bupropion, if injected into amnesic mice against the background of activation of $GABA_A$ and $GABA_B$ receptors, increased LP of passage to 64 ± 13 and 67 ± 14 sec respectively (Fig. 1c, 2, d, 2).

Activation of postsynaptic DA-receptors by (+)-3-PPP in group A3 led to considerable facilitation of CPAR recall, which could be clearly distinguished as an increase in the mean values of LP of passage to 117 ± 12 sec. This effect was long-lasting and when tested on the 8th day LP of passage was statistically significantly longer than in animals receiving physiological saline. If amnesia developed against the background of activation of BD, $GABA_A$- and $GABA_B$-receptors the dynamics of the effect of (+)-3-PPP was modified: the duration was sharply reduced — a statistical ly significant lengthening of LP of passage was recorded only on the day of injection of the drug (Fig. 1b, 3, c, 3, d, 3).

Activation by quinpyrole, a highly selective D-2-receptor agonist, led to restoration of recall of CPAR when disturbed by the amnesia-inducing procedure, without any change in the functional state of the GABA-system (Fig. 1a, 4). Incidentally, the effect of quinpyrole was of short duration. If amnesia developed against the background of activation of $GABA_A$- and $GABA_B$-receptors, recovery of CPAR was less effective (Fig. 1c, 4, d, 4). In group A4, 30 min after injection of the drug, LP of passage was 135 ± 14 sec, whereas in groups C4 and D4 it was only 79 ± 23 and 76 ± 16 sec respectively. On the creation of the neurochemical set by diazepam the period of preservation of improved CPAR recall after injection of quinpyrole was significantly lengthened (Fig. 1b, 4).

The investigation thus showed that activation of BD-, GAB_A-, and $GABA_B$-receptors before training and induction of amnesia did not abolish the basic possibility of withdrawal of the memory trace by activation of the DA-system, while, however, modifying its dynamics. These facts may be explained on the grounds that the main load in the case of a single training session is carried by formations of the limbic system [3], where GABA exhibits relatively weak effects on mesolimbic DA-neurons [5, 7]. Meanwhile the results do not indicate that the DA- and GABA-systems function independently in the process of restoration of memory trace recall when impaired by amnesia. During the formation of the amnesic state against the background of activation of BD-receptors by diazepam, the effectiveness of bupropion is enhanced, the period of preservation of the effect of quinpyrole is significantly lengthened, and both parameters of the effect of (+)-3-PPP are reduced. $GABA_A$- and $GABA_B$-receptors are synergically involved in modulation of recall processes by activation of the DA-system along different channels. Analysis of the results thus provide evidence of the existence of an adaptive mechanism in the DA-system, compensating for the change in regulatory tone of the GABA-system and enabling withdrawal of the memory trace when impaired by amnesia.

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