EFFECT OF TRIFLUOPERAZINE, CARBIDINE, AND IMIPRAMINE ON EVOKED POTENTIALS IN STRUCTURES OF THE LIMBICO-RETICULAR COMPLEX

Academican V. V. Zakusov* and G. N. Krolevets

UDC 612.822.3.014.46:615.21

Experiments on rabbits showed that trifluoperazine and carbidine have a marked depriming effect on evoked potentials in the parvocellular portion of the dorsomedial nucleus, centrum medianum, nucleus reuniens of the thalamus, posterior nucleus of the hypothalamus, and central gray matter in response to stimulation of the sciatic nerve. Conversely, the amplitude of the evoked potentials is increased in the dorsal hippocampus and amygdala (baso-lateral and central nuclei). More marked changes were produced by trifluoperazine than by carbidine. Imipramine has a marked inhibitory effect on evoked potentials in the dorsal hippocampus, the parvocellular part of the dorsomedial nucleus, centrum medianum, and nucleus reuniens of the thalamus. The action of imipramine on evoked responses in the amygdala (baso-lateral and central nuclei), the posterior nucleus of the hypothalamus, and the central gray matter is biphasic: in the first phase the amplitude of the evoked responses is sharply increased, but in the second it is reduced. Evoked responses in the mesencephalic reticular formation are increased to a greater degree by imipramine than by trifluoperazine and carbidine.

An important problem in modern pharmacology is the study of the effect of neurotropic drugs on the functional systems of the brain. The principle of systemic analysis was used in this investigation to study the effects of two neuroleptics – trifluoperazine, carbidine (3,6-dimethyl-1,2,3,4,4a,9a-hexahydro-γ-carboline dehydrochloride) – and the antidepressant imipramine on evoked potentials in structures of the limbic system, the diffuse thalamocortical nonspecific projection system, and the mesencephalic reticular formation (RF).

EXPERIMENTAL METHOD

Acute electrophysiological experiments were carried out on unanesthetized rabbits immobilized with flaxedil (5 mg/kg) and artificially ventilated. Details of the method were described earlier [3]. Evoked potentials were recorded in the parvocellular and magnocellular parts of the dorsomedial nucleus, the nonspecific nuclei of the thalamus (centrum medianum and nucleus reuniens), the posterior nucleus of the hypothalamus, central gray matter, dorsal hippocampus (area CA_1), the amygdala (baso-lateral and central nuclei), and the mesencephalic RF in response to sciatic nerve stimulation (0.01-0.1 msec, 1-10 V). Stereotaxic coordinates of the structures were determined from the atlas [1]. The location of the electrodes was verified morphologically. Altogether 285 rabbits were used in the experiments. Trifluoperazine, carbidine, and imipramine were injected intravenously into the rabbits in doses of 1 and 5 mg/kg.

EXPERIMENTAL RESULTS

Under the influence of trifluoperazine and carbidine the amplitudes of the evoked responses were reduced and their latent periods lengthened in the parvocellular part of the dorsomedial nucleus, centrum

*Academy of Medical Sciences of the USSR.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 77, No. 2, pp. 44-47, February, 1974. Original article submitted April 20, 1973.

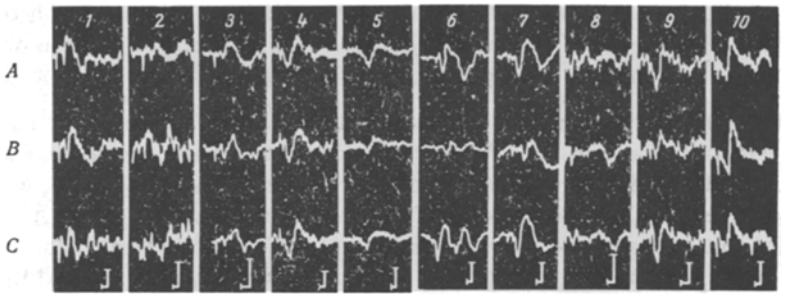

Fig. 1. Changes in evoked potentials in brain structures of the rabbit in response to stimulation of the sciatic nerve after intravenous injection of trifluoperazine (1 mg/kg): 1) hippocampus; 2) central nucleus of the amygdala; 3) baso-lateral nucleus of the amygdala; 4) magnocellular part of dorsomedial nucleus; 5) parvocellular part of dorsomedial nucleus; 6) centrum medianum; 7) nucleus reuniens; 8) central gray matter; 9) posterior hypothalamic nucleus; 10) mesencephalic RF. A) before injection, B) 1 h, C) 3 h after injection of trifluoperazine. Calibration: amplitude 200 V, duration 20 msec.

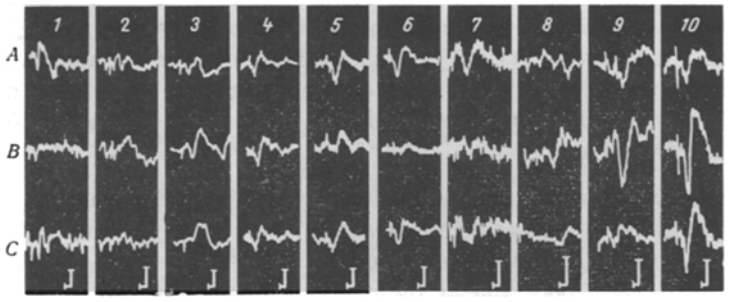

Fig. 2. Changes in evoked potentials in brain structures of rabbit in response to sciatic nerve stimulation after intravenous injection of imipramine (1 mg/kg). Legend as in Fig. 1.

medianum, posterior hypothalamic nucleus, and central gray matter (Fig. 1B: 5, 6, 8, 9). Similar but less marked changes were observed in the nucleus reuniens of the thalamus but the latent period was not lengthened (Fig. 1B: 7). Imipramine also inhibited evoked responses in the centrum medianum and nucleus reuniens (Fig. 2B: 6, 7). The maximal changes in the evoked responses in the parvocellular part of the dorsomedial nucleus, centrum medianum, and nucleus reuniens were observed between 20 and 80 min after the injection of trifluoperazine or carbidine (Fig. 1B: 5, 6, 7). Imipramine inhibited the evoked responses in the parvocellular part of the dorsomedial nucleus by a lesser degree than trifluoperazine (Fig. 2B: 5). Evoked potentials in the magnocellular part of the dorsomedial nucleus were not affected by these drugs (Figs. 1B: 4 and 2B: 4). Meanwhile in the central gray matter and posterior hypothalamic nucleus the maximal depriming effect of trifluoperazine and carbidine appeared between 50 and 240 min after injection of the drugs, i.e., the effect developed more slowly than in the previous case (Fig. 1C: 9). The severity of these changes was greater after the action of trifluoperazine than of carbidine. The effect of impramine on the evoked responses in the posterior hypothalamic nucleus was biphasic: in the first 1-1.5 h the amplitude of the evoked potentials rose (Fig. 2B: 8), but later (second phase) it fell gradually below the initial level (Fig. 2C: 8).

The amplitude of the somatic evoked responses in the baso-lateral and central nuclei of the amygdala was increased by trifluoperazine and carbidine by a greater degree (Fig. 1B: 2, 3) than in the dorsal hippocampus (Fig. 1B: 1). Changes in the evoked potentials in the nuclei of the amygdala after injection of imipramine were biphasic. In the first phase, which lasted from 10 min to 1.5 h, the amplitude of the potentials increased both in the baso-lateral and in the central nucleus of the amygdala (Fig. 2B: 2, 3). The second phase developed during the 2-3 h after injection of the drug: the amplitude of the evoked potentials gradually fell below its initial level (Fig. 2C: 2, 3).

The amplitude of the evoked potentials in the mesencephalic RF increased after injection of trifluoperazine and carbidine (Fig. 1B: 10). An even greater increase in the amplitude of the evoked potentials was recorded 30-50 min after the injection of imipramine (Fig. 2B: 10).

It can be concluded from the analysis of these results that trifluoperazine, carbidine, and imipramine have a well-marked depriming action, of different strength, on certain components of the nonspecific system of the thalamus. Similar results were obtained by Nikolaeva and Kozhin [5], who found a decrease in excitability in the medial nuclei of the thalamus after administration of imipramine. It is interesting to note that, according to data in the literature, the excitability of the thalamic projection system is also reduced after administration of stimulants [9]. Meanwhile trifluoperazine, carbidine, and imipramine do not inhibit evoked responses in the mesencephalic part of RF but, on the contrary, they increase their amplitude; this increase in the evoked responses is greatest after administration of imipramine. Presumably these drugs have no depriming effect on the mesencephalic part of RF whereas imipramine, in doses of 1 and 5 mg/kg, by contrast evidently activates mesencephalic RF [11]. Opinions still differ regarding relations between the diffuse thalamocortical projection system and the ascending nonspecific system [2, 12]. The thalamic and mesencephalic nonspecific systems can presumably function under certain conditions either as a single system or, by contrast, as antagonistic systems. Trifluoperazine, carbidine, and imipramine have opposite effects on evoked potentials in these systems, evidently reflecting the functional independence of these systems during the action of the three drugs studied.

Changes in the evoked potentials in the various structures of the limbic system, which is concerned with the formation of behavioral and emotional responses, deserve particular attention. The hippocampus is known to exert inhibitory control over the structures of the brain stem [6, 7]. Trifluoperazine and carbidine, in the doses used, evidently potentiate the inhibitory effects of the hippocampus on these structures. This hypothesis is based on the results of our previous investigation [4]. Imipramine, on the other hand, weakens the influence of the dorsal hippocampus, thereby sharply inhibiting the local, transcommissural, and somatic hippocampal responses.

The fact that the effects of imipramine on evoked potentials in the amygdala, posterior hypothalamic nucleus, and central gray matter are phasic in character deserves attention. It is interesting to note that the increase in the evoked potentials observed in the first phase takes place parallel with the increase in the responses in RF and with their decrease in the centrum medianum and nucleus reuniens. The effects of imipramine in the amygdala, posterior hypothalamus, and central gray matter during this period are evidently connected with its activating effect. As far as the central nucleus of the amygdala is concerned, this region in turn is known to have a facilitatory effect on structures of the diencephalon and mesencephalon [13]. In the second phase the effects of imipramine in the posterior hypothalamic nucleus and central gray matter come to resemble more closely the effects of trifluoperazine and carbidine. During this period imipramine has an inhibitory effect on the amygdala also.

Trifluoperazine, carbidine, and imipramine thus modify the intracentral relations between the ascending activating, limbic, and thalamocortical nonspecific systems and the relations within these systems themselves. These effects are evidently reflected in the formation of the integrated response of the body during the development of the characteristic effects of neuroleptics and antidepressants.

LITERATURE CITED

1. J. Buresh, I. Petran, and I. Zakhar, Electrophysiological Methods of Investigation [in Russian], Moscow (1962), p. 389.
2. O. Zager, The Diencephalon [in Russian], Bucharest (1962).
3. G. N. Krolevets, Byull. Éksperim. Biol. i Med., No. 12, 47 (1969).
4. G. N. Krolevets, Byull. Éksperim. Biol. i Med., No. 9, 57 (1972).
5. N. I. Nikolaeva and A. A. Kozhin, in: The Pharmacological Basis of the Antidepressant Effect [in Russian], Leningrad (1970), p. 99.
6. R. Douglas and K. Pribram, J. Neurophysiol., 29, 197 (1966).
7. J. D. Green, Physiol. Rev., 44, 561 (1964).
8. P. D. MacLean, J. Nerve Ment. Dis., 127, 1 (1958).
9. M. Monnier and P. Krupp, Arch. Exp. Path. Pharmakol., 238, 227 (1960).
10. J. H. Penaloza-Rojas et al., Exp. Neurol., 4, 205 (1961).
11. H. Rubio-Chevannier et al., Exp. Neurol., 4, 214 (1961).
12. R. Tissot and M. Monnier, Electroenceph. Clin. Neurophysiol., 11, 675 (1959).
13. G. Singer and R. B. Montgomery, Physiol. Behav., 4, 505 (1969).