ANALYSIS OF RECEPTORS FOR CHANGES IN BEHAVIORAL RESPONSES OF CATS CAUSED BY CATECHOLAMINES AND SEROTONIN

I. V. Komissarov and A. N. Talalaenko

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Changes in motor and autonomic components of behavioral responses following injection of catecholamines, serotonin, and their antagonists into the lateral ventricles were investigated in experiments on 31 cats. Noradrenalin, adrenalin, phenylephrine, and serotonin were found to inhibit the motor activity of the animals. Isoprenaline had no such action. Propranolol and morphine had no effect on, while dihyroergotamine and phentolamine shortened the duration of the inhibitory action of noradrenalin, but not of serotonin. Morphine distorted the response to serotonin, so that inhibition of the animals' motor activity was replace by excitation, which was suppressed by dihydroergotamine and LSD. The results demonstrate that motor inhibition due to biological amines is effected via α-adrenergic or muscarine-sensitive serotonin receptors. Inversion of the action of serotonin is due to the effect of the amine on serotonin-sensitive D-receptors of the brain.

Injection of catecholamines and serotonin in large doses into the lateral ventricle of mice [9] and cats [5, 6] or into the cisterna magna of dogs [4] gives rise to sluggishness, general apathy, stupor, analgesia, disturbance of movement coordination, salivation, vomiting, an increased respiration rate, catatonia, and frequently a lethargic type of sleep. The observed effects are not associated with spasm of the cerebral vessels [15] but are probably due to the action of the biological amines on specific adrenergic and serotonin-sensitive systems of the brain [7, 13]. Experiments in which microinjections of adrenalin were given into single units of the hypothalamus and lateral optic tract suggest that the effect of the amine is achieved through α-adrenergic receptors, because inhibition of the bioelectrical activity of these neurons was abolished by dibenamine, phenoxybensamine, and phentolamine, but not by dichloroisoproterenol or propranolol [10, 14]. The nature of the receptors through which the serotonin-induced changes in somatic and autonomic functions are effected is not yet clear. For instance, depression induced by intraventricular injection of serotonin was abolished by morphine, methadone, and amphetamine, but not by BOL or 5-benzyloxygramine [7]. However, only BOL-148 and LSD possessed central antiserotonin properties, for they inhibited electrical activity produced by microinjections of serotonin into single units of the lateral optic tract [14].

The object of the present investigation was to analyze receptors through which the action of catecholamines and serotonin on motor and autonomic components of behavioral responses in cats are effected when these drugs are injected into the lateral ventricles.

EXPERIMENTAL METHOD

Altogether 21 series of experiments were carried out on 31 cats weighing from 2 to 4 kg, 4-5 animals being used in each series. Drugs were injected into the right lateral ventricle through a permanent cannula [5] not more often than once a week. In 2 series of experiments, 5 h before injection of the amines, the

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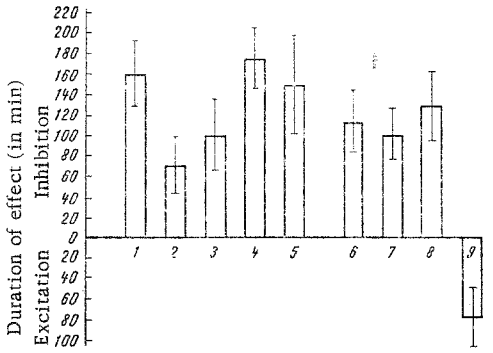

Fig. 1. Effect of phentolamine, dihydroergotamine, propranolol, and morphine on duration of changes in motor components of behavioral responses of cats induced by noradrenalin and serotonin: 1) duration of motor inhibition induced by noradrenalin; 2) ditto, after preliminary injection of phentolamine; 3) ditto, after preliminary injection of dihydroergotamine; 4) ditto, after preliminary injection of propranolol; 5) ditto, after preliminary injection of morphine; 6) duration of motor inhibition induced by serotonin; 7) ditto, after preliminary injection of phentolamine; 8) ditto, after preliminary injection of dihydroergotamine 9) duration of excitation induced by serotonin after preliminary injection of morphine.

animals received an intramuscular injection of iproniazid in a dose of 100 mg/kg. The investigations were carried out in a moderately illuminated room. A note was made of changes in motor activity of the animals during free movement, their autonomic responses (dyspnea, mydriasis, salivation), and responses to external stimuli (clicks, light, the beat of a metronome). To define the disturbances of behavioral responses quantitatively, changes in the duration of motor activity of the animals produced by the test monoamines were estimated. To analyze the receptors through which specific effects of noradrenalin and serotonin (5-HT) are achieved, 20 min before injection of the amines into the ventricle, dihydroergotamine (DET), one of the following drugs was injected: dihydroergotamine (DET), a specific antagonist of the α-effects of catecholamines [11] and the D-effects of serotonin [8], the α-adrenolytic phentolamine [11, 12], the β-adrenolytic propranolol [3], and morphine, which inhibits effects due to the action of 5-HT on serotonin-sensitive M-receptors [8]. The sympathomimetics, serotonin, and their antagonists were injected in a dose of 170 μg (calculated as base) in a volume of 0.2 ml. Cats of the control group received an injection of bidistilled water.

EXPERIMENTAL RESULTS

Limitation of movement, a decrease in muscle tone, and sluggishness were observed 10-15 min after injection of adrenalin, noradrenalin, phenylephrine, and serotonin into the ventricle. At the same time, the animals lost their motor initiative and playfulness, their responses to external stimuli were weakened, and they frequently lay on their side. Inhibition of motor activity continued for 2-2.5 h (Fig. 1). Changes in motor activity correlated with autonomic reactions: dyspnea, mydriasis, salivation. Iproniazid, on the other hand, did not change the animals' behavioral responses: the cats remained playful and continued their motor activity and orienting reactions to visual and acoustic stimuli. No autonomic or locomotor disturbances were present.

Quantitative characteristics of the motor and autonomic components of the behavioral responses due to noradrenalin and serotonin were unchanged if the animals received a preliminary injection of iproniazid, but the duration of the disturbances of behavior was increased to 6-8 h.

Injection of DET, phentolamine, propranolol, and morphine (170 μg) into the lateral ventricle had no significant effect on the behavioral responses of the cats. DET and phentolamine had no effect on the motor and autonomic components of the behavioral changes induced by serotonin, but significantly shortened the period of motor inhibition due to noradrenalin. Propranolol and morphine,on the the other hand, changed neither the duration nor the qualitative characteristics of the inhibitory effect of noradrenalin on the cats' behavioral responses (Fig. 1).

After preliminary injection of morphine, injection of 5-HT into the ventricle produced restlessness, alertness, and a resumption of brisk motor activity. The cats shook their heads and ears vigorously and mewed loudly. Excitation induced by serotonin was replaced from time to time by periods of hypokinetic rigidity: if the animals were moving they stopped suddenly, sat on their paws, and looked fixedly at the same point, and they did not respond, or responded only weakly, to external stimuli. In such cases the animals' state was very similar to catatonic stupor. When an attempt was made to lift the cat, it tried to tear itself away from the hand, and once it was free, it took a few steps and then suddenly stopped and looked around on all sides. These disturbances reached their maximum during the first 30-40 min, and then gradually disappeared during the next hour, being replaced by motor inhibition.

DET (170 μg) in 4 experiments or LSD (20 μg) in 2 experiments, after preliminary injection into the ventricle mixed with morphine (170 μg), suppressed the excitation produced by serotonin. Under these conditions the cats movements were restricted, their motor initiative was diminished, but they remained capable of moving and their muscle tone continued to be high and their responses to external stimuli were well marked.

Despite the similarity between changes in behavioral responses due to sympathomimetics and serotonin, the mechanism of the inhibitory effect of catecholamines is not identical with that of 5-HT. This is true at least in the respect that their points of application of their primary action in the brain are different. Judging from the effect of propranolol on that of noradrenalin, and the absence of changes in behavioral responses of the cats to injection of iproniazid, it is doubtful whether β-receptors play any part in the observed effects of noradrenalin. The more likely hypothesis is that the action of this amine is effected through α-adrenergic receptors. This view is confirmed by experiments in which α-adrenolitics were shown to shorten the period of motor inhibition due to noradrenalin. Further support is given by the results of experiments showing that the suppression of spontaneous unit activity in the hypothalamus and lateral optic tract by noradrenalin was abolished by dibenamine, phenoxybensamine, and phentolamine, but not by propranolol or dichloroisoproterenol [10, 14]. On the other hand, motor inhibition induced by serotonin was not connected with the action of the amine on α-adrenergic receptors, for it was not abolished by phentolamine and DET. On the contrary, blocking of serotonin M-receptors by morphine distorts the effect of 5-HT on behavior, so that the animals become excited. It is important to emphasize that the "inversion" of serotonin action thus discovered is specific, for the corresponding inhibitory effect of noradrenalin is unchanged by morphine. These results can be satisfactorily explained on the assumption that the depriming effect of 5-HT is due to its action on serotonin M-receptors, blocking of which by morphine reveals the excitatory action of the amine, effected through D-receptors. These ideas correlate also with the weakening of some types of intracentral inhibition by morphine [1, 2], and they are confirmed by experiments showing the ability of DET and LSD, which selectively block serotonin D-receptors [8], to suppress the motor excitation and also the catatonia produced by serotonin.

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