ONSET OF VOMITING AFTER MICROINJECTIONS OF SEROTONIN INTO THE HYPOTHALAMUS, SEPTUM, AND AMYGDALA OF CATS RECEIVING IMIPRAMINE

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UDC 615.214.32.015.2:615.362.018:547.576

Microinjection of serotonin solution directly into the hypothalamus, septum, and amygdala of cats after preliminary intramuscular injection of imipramine caused vomiting. Against a background of benactyzine, vomiting did not develop. Microinjection of acetylcholine into the same structures after intramuscular injection of benactyzine, but not of imipramine, produced a prevomiting state.

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Data in the literature on the effect of antidepressants of the imipramine group on metabolism and effects of serotonin in the central nervous system and at the periphery are conflicting [3, 4]. Both antagonism and synergism with serotonin have been described. In phenomena when imipramine and other antidepressants potentiate the effects of noradrenalin (contraction of the nictitating membrane and elevation of the blood pressure in cats, hyperthermia in rabbits and rats), they potentiate the same effects of serotonin [3, 11].

Although facts concerning synergism of imipramine and noradrenalin were used as long ago as in 1959 by Sigg in his widely acclaimed hypothesis of the adrenosensitizing mechanism of the antidepressive action of imipramine [3, 4], potentiation of the effects of serotonin have been almost completely ignored.

The synergism between imipramine and serotonin is interesting mainly because of clinical data showing that tryptophan (especially against a background of monoamine oxidase inhibition) is capable of elevating the mood of psychiatric patients [8, 9, 13, 14]. Antagonism with serotonin may be important in the action, not of antidepressants, but of neuroleptics [5, 15].

The facts described above cannot be reconciled with the hypothesis put forward by Brody and coworkers, the only "serotonin" hypothesis. On various grounds these workers postulated that the antidepressive effects of imipramine is based on its antagonism with free serotonin in the brain and on the resulting shift in the balance of the trophotropic and ergotropic systems toward predominance of the latter. A critical examination of Brody's hypothesis has been published previously [3].

Serotonin is distributed irregularly in the brain of animals and man [7, 12], and its content is particularly high in the hypothalamus and limbic structures playing a leading role in control of the emotions [1, 2, 10]. The function of serotonin in these structures is unknown.

In face of these facts we decided to investigate the action of imipramine on effects of serotonin when injected directly into the limbic structures and hypothalamus.

EXPERIMENTAL METHOD

Chronic experiments were performed on 15 adult cats allowed to move freely in a chamber measuring 100 × 120 × 90 cm. Solutions were injected into the brain structures by means of an injection system consisting of an external directing needle (10 mm), an internal injecting needle, a polyethylene tube (140 cm), and a microinjector. Two or three directing needles were inserted into each cat (by means of a stereotaxic apparatus) and fixed with acrylic glue.

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TABLE 1. Frequency of Vomiting after Microinjection of 2% Serotonin Solution

Preparations injected intramuscularly 45 min before serotonin		Amygdala, central and dorsal region	Septum, central and ventral region	Hypothalamus, preoptic and anterolateral region
Physiological saline		0/14	0/16[2]	0/19
Imipramine	1 mg/kg	0/3	0/3	2/7
	5 mg/kg	–	3/5	3/4
	10 mg/kg	1/2	1/1	–
Benactyzine	0.5 mg/kg	0/4[1]	0/3	1/4
	1 mg/kg	0/5	0/4	0/4

Note. Number of experiments in which vomiting observed shown in numerator, total number of experiments in denominator (1 control and 2-3 experimental tests in each experiment).
[1]In two experiments a prevomiting state was observed.
[2]In one experiment, a prevomiting state was observed after injection of 200 μg serotonin.

Sterile 2% solutions of acetylcholine chloride and serotonin-creatinine sulfate in physiological saline ere made up immediately before the experiment, and 0.5-1% solutions of imipramine hydrochloride and enactyzine hydrochloride were injected intramuscularly. From 10 to 14 days after the operation, after ıe cats had become accustomed to the experimental environment, a thin injection needle of the required ength, preliminarily connected by the polyethylene tube to the microinjector and filled with acetylcholine r serotonin solutions or with physiological saline, was inserted through the directing needle into one of the rain structures (the hypothalamus, septum, or amygdala). The first intracerebral injection of serotonin or acetylcholine) in a volume of 0.005 ml was given 15 min after insertion of the needle. The animal's ehavioral and autonomic responses were recorded and photographed. Sometimes the injection was re-eated after 15 min in order to determine the stability of the effect. Imipramine (1-5 or 10 mg/kg) or enactyzine (0.5 and 1 mg/kg), or physiological saline (in control experiments) was injected intramuscularly) min after microinjection of serotonin (or acetylcholine or physiological saline) into the brain. Next, 45 in after, a second microinjection of serotonin (acetylcholine, physiological saline) was given into the brain.

As a control of nonspecific factors of stimulation, microinjections of physiological saline (0.005-02 ml) with the same pH as the solutions of serotonin and acetylcholine, were given. Each point of in-ction into the brain was investigated not more than 4-5 times, including 1-2 control experiments and 3-4 periments in which solutions of acetylcholine and serotonin were injected.

After the end of the experiments the localization of the tip of the injection needle in all brain struc-res was verified histologically.

EXPERIMENTAL RESULTS AND DISCUSSION

Microinjections of serotonin into the hypothalamus, septum, and amygdala caused negligeable auto-mic responses: licking, sometimes salivation, chewing. Vomiting was never observed, even after 3 suc-ssive injections of serotonin at intervals of 15-30 min. After intramuscular injection of imipramine, icroinjections of serotonin caused vomiting (Table 1).

After administration of imipramine (1 mg/kg), serotonin caused vomiting only in the case of micro-ection into the hypothalamus, possibly indicating the somewhat greater sensitivity of this structure to a mbination of imipramine and serotonin. After administration of benactyzine (0.5-1 mg/kg), with one ex-ption serotonin did not cause vomiting.

After preliminary administration of 5 and 10 mg/kg imipramine, microinjection of serotonin pro-ced vomiting 1-2 min later. The animals developed signs of motor excitation, salivation, frequent spasms the mouth muscles, followed by a typical prevomiting pose with the forelimbs straight and wide apart

and the trunk leaning forward. In all animals, including those which did not vomit, serotonin administered after imipramine caused marked intensification of autonomic reactions: salivation, licking, quickening of respiration.

In 5 of the 25 experiments during which imipramine was injected vomiting was observed, coming on 5-12 min after injection, i.e., before the second microinjection of serotonin. No emetic effect of imipramine itself was observed in previous experiments [7] in which cats received a single or several injections of the same dose of the preparation, and none have been described in the literature. We attribute the emetic effect of imipramine in our experiments to summation of chemical stimulation of the brain structures by the initial (control) injection of serotonin and to the sensitizing action of imipramine on these structures.

In another series of experiments acetylcholine was injected into the same three brain structures of the same cats.

Against the background of preliminary intramuscular injection of benactyzine (0.5-1 mg/kg), microinjections of acetylcholine into the hypothalamus and septum, but not into the amygdala, intensified autonomic responses and the prevomiting state in most animals. This effect of potentiation of the action of acetylcholine can hardly be explained by the choline-sensitizing action of benactyzine, because relatively large doses of the drug were given (0.5-1 mg/kg).

Hence, during local chemical stimulation of brain structures, a definite difference can be found between the effects of imipramine and benactyzine, preparations exhibiting a qualitatively similar action in most pharmacological tests for antidepressants. This difference is the more marked because it was found in the relationship between imipramine and benactyzine, on the one hand, and serotonin and acetylcholine, chemical factors of the trophotropic system whose effects are blocked by cholinolytics, on the other hand.

Potentiation of autonomic responses of serotonin by the action of imipramine in the hypothalamus and septum may have some relation to the antidepressive action of the drug and it merits more attention than it has hitherto received, for interest has been concentration almost entirely on adrenergic and cholinergic systems [3, 4, 9].

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