EXPERIMENTAL STUDY OF THE TRANQUILIZING AND ANTIDEPRESSANT ACTION OF THE CENTRAL CHOLINOLYTICS

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Hyperemotional and depressed states were simulated in rabbits by stimulation of the hypothalamus and medial parts of the septal zone. In small doses, central cholinolytics exhibit a tranquilizing action, depressing the emotional state into responses of aggressive and defensive behavior, disturb intraseptal relationships by blocking the effects of stimulation of the lateral portions of the septum, and facilitate detection of the inhibitory effect of the medial portions of the septum. In large doses they depress inhibitory septal effects, and this may be connected with their antidepressant action.

There is clinical evidence that the central cholinolytics possess both tranquilizing and antidepressant properties [5, 9]. However, the mechanism of this pharmacotherapeutic effect has not been adequately studied, and the experimental data are largely contradictory, a fact attributable partly to inadequacy of the experimental psychopharmacological methods used and partly to underestimation of the importance of intracentral changes in determining the effects of central cholinolytics.

When the action of the central cholinolytics is analyzed it must be remembered that the diencephalon, which coordinates the somatic and autonomic manifestations of emotional behavior, is under the modulating influence of the paleocortex. Inhibitory influences are spread principally through the septum; destruction of the septum facilitates locomotor activity and aggressiveness [2, 13, 15], and its stimulation inhibits emotional reactivity and motor activity in animals [1].

The object of this investigation was to study the tranquilizing and antidepressant action of a series of central cholinolytics (methyldiazine, benactyzine, and scopolamine) on models of emotional excitation and depression elaborated previously [4, 7, 8], and to determine the link between this action and changes in intracentral (septo-hypothalamic and intraseptal) regulatory interrelationships.

EXPERIMENTAL METHOD

Observations were made on 32 rabbits with electrodes implanted into the posterior portions of the hypothalamus and the medial and lateral portions of the septum. Stimulation was applied alternately to the hypothalamus (300/sec, 30 sec, 1-3 V) and to the septum (10-30/sec, 3 min, 1-2 V), and also to pairs of structures of both zones in different combinations. Thresholds of excitation, latent periods, and the intensity of motor and autonomic manifestations were recorded; the general significance of the response and its relevance to the situation were also considered.

Stimulation of the periventricular nuclei of the hypothalamus was accompanied by the appearance of a hyperemotional state, aggressiveness, and increased motor activity (the aggressive-defensive reaction) [6], and these were used as a model for studying the tranquilizing action. Stimulation of the medial portions of the septal zone was accompanied by a lowering of emotional reactivity and the development of depression

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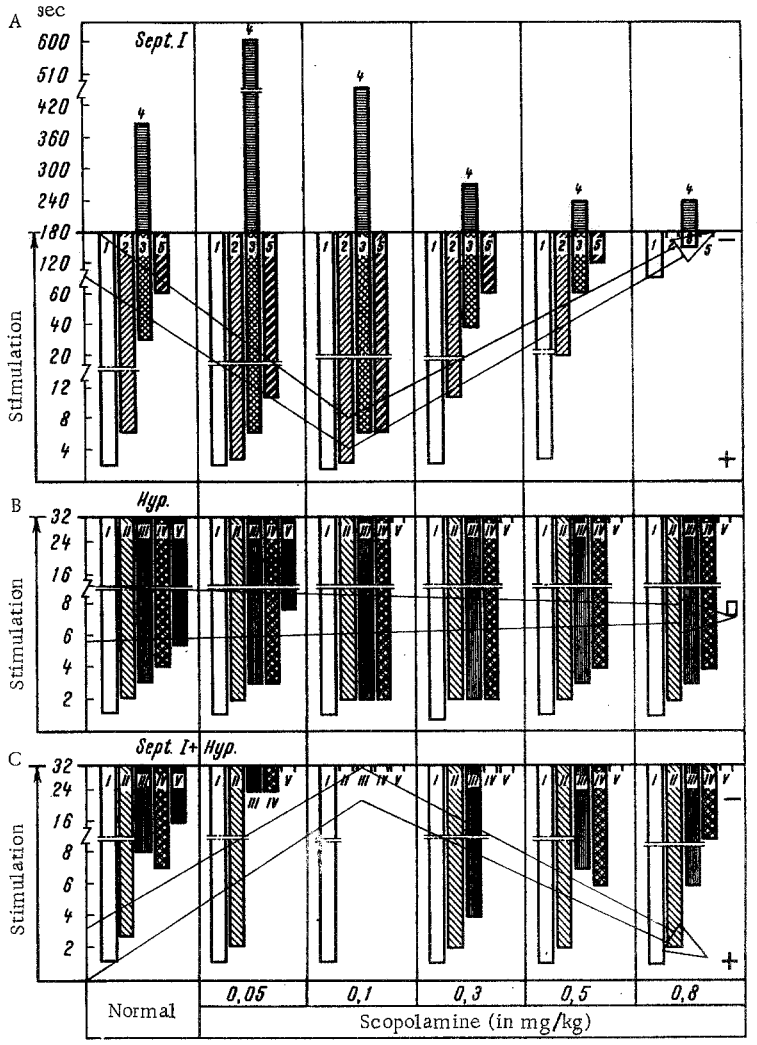

Fig. 1. Changes in behavioral reactions produced by increasing doses of scopolamine: A) septal inhibitory reaction of type I; B) hypothalamic reaction of aggressive and defensive type; C) course of aggressive and defensive reaction against the background of preliminary stimulation of medial portions of the septum. Direction of changes in reactions after administration of scopolamine indicated conventionally by arrow: downward—facilitation; upward—inhibition; horizontally—no change. Columns represent separate components of reactions corresponding to numeration in text. Column 4 shows duration of "lateral position" in period immediately after stimulation. Duration of stimulation (in sec) shown along ordinate by arrow. Interval from beginning of stimulation to beginning of columns represents latent period.

and inhibition, which were used as the model for studying the antidepressant action. Paired stimulation was used to study septo-hypothalamic and hypothalamo-septal intracentral interrelationships and the effect of the central cholinolytics on them.

EXPERIMENTAL RESULTS AND DISCUSSION

The response to stimulation of the posterior hypothalamus was characterized by a series of consecutively developing components, which are represented graphically in Fig. 1B. Alerting (I), changing position (II), jumping, turning, or running (III-IV), and quickening of respiration and dilatation of the pupils could be

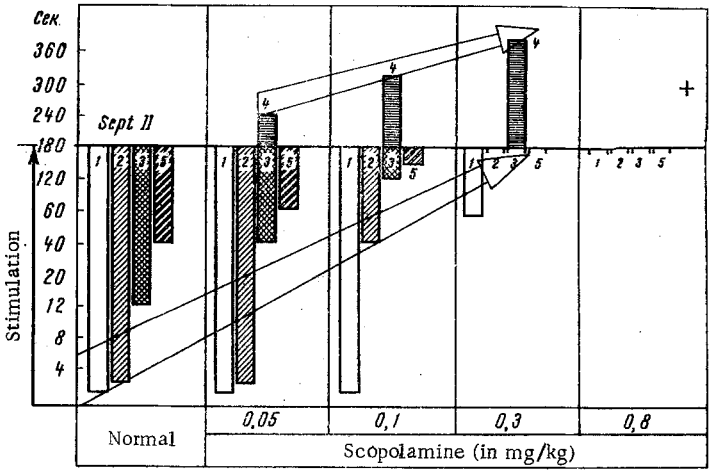

Fig. 2. Effect of increasing doses of scopolamine on response to stimulation of lateral portions of septum. Legend as in Fig. 1.

classed as the combined somatic and autonomic "expression" of the emotional reaction, whose anatomical basis is localized in the diencephalic and mesencephalic structures [10-12]. Goal-directed aggressiveness and a hyperemotional state (V) are classed as "emotional states," located anatomically in neo- and paleocortical structures [3].

Small doses of methyldiazine (0.01-0.05 mg/kg), benactyzine (0.05-0.1 mg/kg), and scopolamine 0.1 mg/kg) completely suppressed the emotional state. Although stimulation of the hypothalamus evoked, as before, the whole series of somatic and autonomic manifestations of the reaction, the rabbit no longer exhibited aggressiveness, and its movements lost their purposiveness. The motor components of the reaction (jumping, turning, aimless running) were sometimes facilitated (shortening of the latent periods, lowering of the thresholds of excitability, increase in intensity). Suppression of the somatic and autonomic manifestations of the hypothalamic reaction evidently requires much larger doses, for within the range tested (up to 1 mg/kg) no appreciable inhibition of these responses was observed. The effect of scopolamine on individual components of the aggressive-defensive reaction is illustrated in Fig. 1B.

The anatomical basis of the "emotional expression" is thus relatively resistant to the action of the central cholinolytics, whereas the paleocortical systems of the brain, which integrate the emotional state, are inhibited by small doses. This is largely responsible for the tranquilizing effect of the central cholinolytics.

If only the motor manifestations ("panic running") are used as the index of aggressive and defensive behavior, as was done in other investigations [14, 17], no tranquilizing effect of the central cholinolytics can be demonstrated. This explains the contradictory nature of results described in the literature.

Stimulation of the septum evoked two main types of response, in each of which the components represented graphically in Figs. 1A and 2 could be identified.

The reaction in response to stimulation of the medial portions of the septum (nucleus of the diagonal band, medial septal nucleus (Fig. 1A, type I) was characterized by cessation of spontaneous movements (1), slowing of respiration (2), lowering of muscle tone (3), changing to the "lateral position" (4) when stimulation ended, and depression of the emotional state (5), expressed as a lowering of reactivity to the surrounding situation and to provocatory stimuli, and the development of a state resembling sleep.

Scopolamine and benactyzine, in doses of 0.05-0.1 mg/kg, strengthened the type I septal reaction, as was manifested by the more rapid development (shortening of latent periods) and increased intensity of all components of the response. The results given in Fig. 1A show that under the influence of small doses of scopolamine, the latent period of the lowering of muscle tone (3) is greatly reduced (by 20-30 sec), the duration of the "lateral position" (4) is increased by 2.5-3 min, and the depth and the rate of onset of the state of depression are increased (the latter by 50-60 sec) (5). In large doses (0.3-0.5 mg/kg, these compounds inhibit the development of the type I septal reaction (lengthen latent periods and decrease the intensity of its manifestations), while in doses of 0.8-1 mg/kg they suppress it completely.

The response to stimulation of the ventrolateral nuclei of the caudal portion of the septum (lateral septal nucleus and the adjacent nucleus of the fimbria) (Fig. 2, type II) differed both in its external expression and in its significance, and it was characterized by an initial "stop" reaction (1), quickening of respiration (2), an increase in muscle tone (3), and catatonia (5).

Scopolamine and benactyzine, in doses of 0.05–0.2 mg/kg, weakened the intensity of the manifestations of this reaction; the latent periods of the individual components were increased. Parallel with depression of the type II septal reaction, effects characteristic of type I appeared in the period of stimulation. The muscle tone was lowered a little, and the rabbit could assume the "lateral position" (4). In large doses (0.5–0.8 mg/kg), scopolamine and benactyzine completely suppressed the response to stimulation of the lateral portions of the septum (Fig. 2).

Weakening of the manifestations of the type II septal reaction was not due to depression of the reticular formation of the brain stem, through which the activation of respiration is mediated, for the increase in descending facilitation of muscle tone, as well as the manifestations arising in response to stimulation of the posterior hypothalamus, were undisturbed by scopolamine and benactyzine in these doses.

Hence, scopolamine led to some degree of strengthening of the septal type I inhibitory response in doses weakening the type II septal reaction. On this basis a change in intraseptal interrelationships was postulated.

The effect of scopolamine in intraseptal interrelationships was clearly revealed in the case of mixed reactions, when the stimulating electrode entered intermediate structures between the medial and dorsolateral nuclei of the septal zone. Manifestations of the response in these cases included features of both types of septal reactions. Scopolamine (0.05–0.1 mg/kg) and benactyzine (0.01 mg/kg) inhibited those manifestations of the mixed reaction whose genesis was associated with the lateral portions; as a result, effects characteristic of the type I inhibition reaction, associated with stimulation of the medial portions of the septum, began to predominate.

Facilitation of the type I inhibitory reaction, appearing after administration of small doses of central cholinolytics, can thus be interpreted as the result of a disturbance of intraseptal interrelationships. Strengthening of septal inhibition under the influence of these compounds takes place within the dose range which also inhibits the emotional state in the aggresive-defensive type of response, and it may also be related to the tranquilizing properties of the central cholinolytics. However, it still cannot be concluded that depression of the emotional state is due entirely to strengthening of the inhibitory influences of the septum.

In response to combined stimulation of the medial portions of the septum and the posterior hypothalamus, inhibition of the aggressive-defensive reaction developed, as expressed by an increase in the latent periods of the individual components of the reaction (Fig. 1C) or by complete suppression of the emotional state. The degree of this inhibition depended on the intensity of stimulation, and for this reason the strength of the inhibitory influence of the medial septal zone could be estimated quantitatively before and after administration of the central cholinolytics.

In small doses (0.05–0.1 mg/kg), benactyzine and scopolamine strengthened the inhibitory influence of the medial portions of the septum on the aggressive-defensive behavioral reaction of the posterior hypothalamus (Fig. 1C), which was completely suppressed. Only the initial alerting reaction remained. In large doses (0.3–0.5 mg/kg), benactyzine and scopolamine abolished the inhibitory influence of the septum relative to the somatic and autonomic expressions of the hypothalamic response, and actually facilitated (especially scopolamine) the emotionally expressive movements associated with hypothalamic stimulation. However, the emotional state (purposive aggressiveness, hyperemotional state) was not restored, for its integration is effected not by the hypothalamus, but at the paleocortical level.

The most characteristic feature of the action of large doses of scopolamine and benactyzine is thus their depressant action on septal inhibitory influences, aimed principally in a caudal direction, and this feature may have a bearing on the antidepressant properties of the central cholinolytics. During simulation of a depressive state by stimulation of the medial portions of the septum, this effect is exhibited particularly clearly.

The results of this investigation provide a factual basis for the hypothesis [1] that the antidepressant effects of central cholinolytics may be associated with the removal of inhibitory influences of the septum on the amygdala and hypothalamus. Following the demonstration of cholinergic neurons in the septal zone [16, 18], these effects can be linked with the action of the cholinolytics on cholinergic elements.

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