POTENTIALIZATION OF HYPNOTICS AND ANESTHETICS BY CENTRAL CHOLINOLYTICS

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Investigations carried out by foreign and Russian scientists [1, 2, 5-13] have shown that many of the new cholinolytic agents generally designated as atropine simulants possess an ability to block the cholinergic structures of the central, as well as the peripheral, nervous system; in fact, the cholinolytic effect of some of these preparations is predominantly central. S. V. Anichkov has proposed that such substances (Difacyl, Diazyl, Pentaphene, Tropacine, Methyldiazyl, Aprophene, etc.) be specifically classified as central cholinolytics.

As we [3, 4] and the authors mentioned above have shown, in certain doses, central cholinolytics have a pronounced inhibitory effect on the brain, disturbing higher nervous activity, altering bioelectric activity and preventing arecoline and nicotine convulsions. In [5], S. S. Krylov, having studied the effects of Difacyl and Diazyl on the higher nervous activity of dogs, suggested the possibility of using these substances in combination with hypnotics.

We believe the study of how central cholinolytics influence the effects of hypnotic and anesthetic substances, with a view toward determining the possibility of their combined use to be of definite theoretical and practical interest.

METHOD

Experiments were performed on 1,000 white mice (males weighing 18-20 g) and 20 rabbits. The hypnotic and anesthetic substances used were Barbamyl, chloral hydrate, Hexenal and thiopental.

The central cholinolytics tested were: Difacyl (diphenylacetic acid β-diethylaminoethyl ester hydrochloride), Methyldifacyl (diphenylacetic acid β-diethylaminoisopropyl ester hydrochloride), Diazyl (benzilic acid β-diethylaminoethyl ester hydrochloride), Methyldiazyl (benzilic acid β-diethylaminoisopropyl ester hydrochloride), Aprophene (diphenylpropionic acid β-diethylaminoethyl ester hydrochloride), Tiphen (thiodiphenylacetic acid β-diethylaminoethyl ester hydrochloride), Diprophene (thiodiphenylacetic acid β-dipropylaminoethyl ester hydrochloride), IEM-268 (diphenylacetic acid β-dimethylaminoisopropyl ester hydrochloride), Pentaphene (phenylcyclopentacarbonic acid β-diethylaminoethyl ester hydrochloride), thioester 22 (thiobenzilic acid β-diethylaminoethyl ester hydrochloride) and Tropacine (diphenylacetic acid tropinic ester hydrochloride).

The force of the effects induced by the anesthetic and hypnotic substances was determined from the degree of decrease in the animal's motor activity as well as from the duration of the sleep or anesthesia; we used the so-called lateral position of the animals as an index of the onset and duration of the sleep or anesthesia, by which we mean the period during which the animals were unable to turn over from their sides to their stomachs and take the position most usual to them.

Each experiment was performed on two different groups of animals simultaneously, each group containing 10-20 animals; one of these groups received only the anesthetics (control group), while the other was given the same dose of anesthetic 5-10 minutes after the administration of the central cholinolytics. Experiments using anesthetics in combination with the central cholinolytics were also conducted with rabbits; in these experiments, we determined the general condition of the animals and recorded the bioelectric activity of the brain.

RESULTS

Experiments on Mice. Chloral hydrate, intraperitoneally injected in doses of 250 mg/kg, decreased the motor activity of some animals (35%) and induced sleep ("lateral position") in 3-5 out of 20 mice. In the control group of 100 mice, the average duration of the "lateral position" equaled 10 minutes. In a dose of 300 mg/kg, chloral hydrate induced a hypnotic effect lasting 15-30 minutes in all the control animals.

The central cholinolytics (listed above), injected intraperitoneally in doses of 5-10 mg/kg, had no apparent effect on the general behavior and condition of the animals. When 250 mg/kg chloral hydrate was injected on a background of the action of central cholinolytics, we observed a considerable increase in the period of decreased motor activity in the experimental animals and an intensification of chloral hydrate's anesthetic effect: All or the majority of

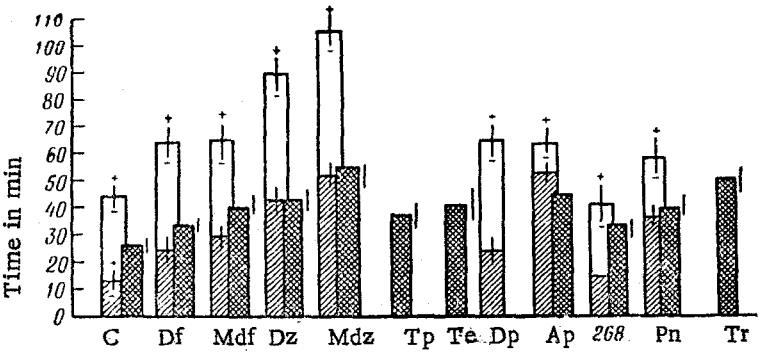

Fig. 1. Influence of central cholinolytics on the hypnotic effect of chloral hydrate. (Average data compiled from 20 observations in each experiment and 220 observations in the control.) White colums) time (in minutes) of reduced motor activity; diagonally striped columns) duration of "lateral position" of animals after intraperitoneal administration of 250 mg/kg chloral hydrate; cross-hatched columns) duration of "lateral position" of animals after intraperitioneal administration of 300 mg/kg chloral hydrate. C) control; Df) Difacyl; Mdf) Methyldifacyl; Dz) Diazyl; Mdz) Methyldiazyl; Tp) Tiphen Te) thioester 22; Dp) Diprophene; Ap) Aprophene; 268) preparation IÉM-268; Pn) Pentaphene; Tr) Tropacine (given intraperitoneally in a dose of 5 mg/kg 10 minutes before the administration of chloral hydrate in both cases).

the experimental animals which had received chloral hydrate and a central cholinolytic were in the "lateral position" for 20-50 minutes. The most intensified hypnotic effects were observed when chloral hydrate was combined with Methyldiazyl, Aprophene or Tropacine (Fig. 1).

In the experiments in which chloral hydrate was used in a dose of 300 mg/kg on a background of the action of central cholinolytics, the same definite intensification of the hypnotic effect as compared with that in the control was observed. Although the two different doses of chloral hydrate (250 and 300 mg/kg) induced "lateral positions" of different durations (10 and 25 minutes) in the control, the duration of the hypnotic effect induced by these two doses of chloral hydrate in combination with the central cholinolytics, used in the same dose in either case, was about the same, i.e. 2-5 times stronger than in the control (see Fig. 1). We consider this evidence that central cholinolytics can potentialize the action of hypnotics.

Barbamyl was tested in one dose, 100 mg/kg, administered to the mice intraperitoneally; in the control animals, this dose induced partial anesthesia lasting more than 60 minutes. If central cholinolytics were administered (5 mg/kg) before the Barbamyl, the latter's effect became almost twice as strong (Fig. 2). Barbamyl's effect was still further intensified by the administration of the cholinolytics in a higher dose (10 mg/kg). It was interesting that although the cholinolytics did not induce a hypnotic effect when used alone in this dose, the hypnotic effect of Barbamyl was approximately doubled, i.e., increased according to the increase in the cholinolytic dose.

Hexenal and thiopental were also injected intraperitoneally in doses which did not themselves induce a hypnotic effect (10 and 5 mg/kg). As a rule, Hexenal and thiopental, administered in these doses 5-10 minutes after the administration of the central cholinolytics, induced anesthesia lasting 5-30 minutes in all the experimental mice. We include the results of the experiments with Hexenal by way of example (see Table).

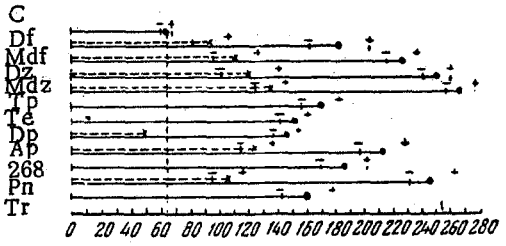

Fig. 2. Change in duration of "lateral position" of mice effected by central cholinolytics in various doses. Solid line) average duration (in minutes) of "lateral position" of mice (20 in each experiment and 180 in control) given 100 mg/kg Barbamyl intraperitoneally 10 minutes after the central cholinolytics (used in a dose of 10 mg/kg); dotted lines) the same on a background of the action of the central cholinolytics injected intraperitoneally in a dose of 5 mg/kg. Same abbreviations used for the preparations as in Fig. 1.

Potentialization of Hexenal's Hypnotic Effect by Central Cholinolytics (5mg/kg)

Preparation	Duration of anesthesia (in minutes) animal number										M	±m	T
	1	2	3	4	5	6	7	8	9	10			
Hexenal (10 mg/kg)	0	0	0	0	0	0	0	0	0	0	0	—	—
Difacyl and Hexenal	6	7	9	14	13	7	14	12	12	12	10,3	3,9	2,6
Methyldifacyl and Hexenal	5	5	13	17	9	10	9	19	18	27	13,2	5,1	2,6
Diazyl and Hexenal	8	12	15	15	27	7	9	16	21	24	15,4	5,8	2,7
Tiphen and Hexenal	8	7	7	9	6	5	7	7	6	8	7,0	2,5	2,8
Methyldiazyl and Hexenal	19	18	17	46	29	20	18	21	24	21	23,4	8,5	2,8
Thioester 22 and Hexenal	17	16	17	14	12	10	10	13	7	36	15,2	6	2,5
Aprophene and Hexenal	12	15	15	25	14	22	6	33	32	6	18,0	7	2,6
Pentaphene and Hexenal	7	38	9	7	54	9	10	19	7	9	17,9	8	2,2
Tropacine and Hexenal	20	14	14	12	22	7	15	8	20	21	15,8	5,6	2,8

Experiments on Rabbits. The influence of central cholinolytics on the effects of hypnotics and anesthetics was studied on rabbits in two types of experiments. In one set of experiments, the force of the anesthetic effect was judged according to the duration of the "lateral position", as in the experiments on mice; in the other set, it was judged according to change in the bioelectric activity of the brain.

The intravenous injection of Hexenal (10 mg/kg) and thiopental (5 mg/kg) induced partial anesthesia lasting 1-4 minutes in 2-3 out of 10 rabbits. The administration of these substances 5 minutes after the administration of central cholinolytics induced an anesthetic effect lasting 5-30 minutes.

Electroencephalographic investigations, performed on rabbits given subanesthetic and anesthetic doses of chloral hydrate, Barbamyl, Hexenal and thiopental and the central cholinolytics in combination with these substances, confirmed the data obtained in the previous experiments on mice and rabbits regarding the potentializing influence of central cholinolytics on the effects of hypnotics and anesthetics.

The intravenous injection in the specified doses of chloral hydrate (100 mg/kg), Barbamyl (35 mg/kg), Hexenal (15 mg/kg) and thiopental (10 mg/kg) induced partial anesthesia of varying duration. At this time, the electroencephalogram (EEG) showed the changes characteristic of this condition: disappearance of the fast potentials, development of slow, high-amplitude waves and, if there was a considerable degree of anesthesia, general inhibition of the bioelectric activity of the brain (Fig. 3, 2).

In subanesthetic doses (75 mg/kg chloral hydrate, 25 mg/kg Barbamyl, 10 mg/kg Hexenal), these preparations did not induce a hypnotic or anesthetic effect; the animals remained lively, and the EEG showed no signs of inhibition of the brain's bioelectric activity (Fig. 3, 4).

Although the central cholinolytics, administered intravenously in doses of 1-5 mg/kg, caused definite changes in the spontaneous bioelectric activity of the brain (Fig. 3, 6), i.e., the appearance of slow waves and a decrease of high-frequency potentials, they were not the changes characteristic of a condition of sleep, especially since the behavior or the rabbits showed no outward signs of sleep.

Small doses of the hypnotics and anesthetics administered intravenously after the central cholinolytics caused sleep and partial anesthesia, and the EEG (Fig. 3, 7) showed changes very similar to those observed with the use of the larger doses of the hypnotics and anesthetics.

In the investigations carried out on mice and rabbits, we obtained statistically authentic data to the effect that central cholinolytics (Difacyl, Methyldifacyl, Aprophene, Pentaphene, Tropacine, etc.) in the specified doses potentialize the hypnotic effect of anesthetics and hypnotics. This was demonstrated by the fact that the cholinolytics, which had no hypnotic effect when used alone, promoted the development of sleep and partial anesthesia when combined with doses of the hypnotics and anesthetics too small to induce a hypnotic effect by themselves (see Figs. 1-3).

This position is further confirmed by the fact that one specific dose of a hypnotic (100 mg/kg Barbamyl, for example) could produce effects of different force and duration depending on the dose of the cholinolytics administered before it. The administration of the cholinolytics in a double dose almost doubled the duration of the sleep induced by Barbamyl, although the cholinolytics themselves had no hypnotic affect in these doses.

The clearly expressed intensifying influence of the central cholinolytics on the hypnotic and anesthetic effects of Hexenal, thiopental, chloral hydrate and Barbamyl is closely connected with the central cholinolytic activity of the preparations. This is indicated by the difference in the effect induced by preparations IÉM-268 and Diprophene from that induced by Diazyl and Aprophene. The cholinolytic effect of the former on the central cholinergic systems is weak, and their potentializing influence on the hypnotic effect is slight.

The greatest potentialization of the effect of hypnotics and anesthetics occurred under the influence of Diazyl, Methyldiazyl, Tropacine and Aprophene, preparations which

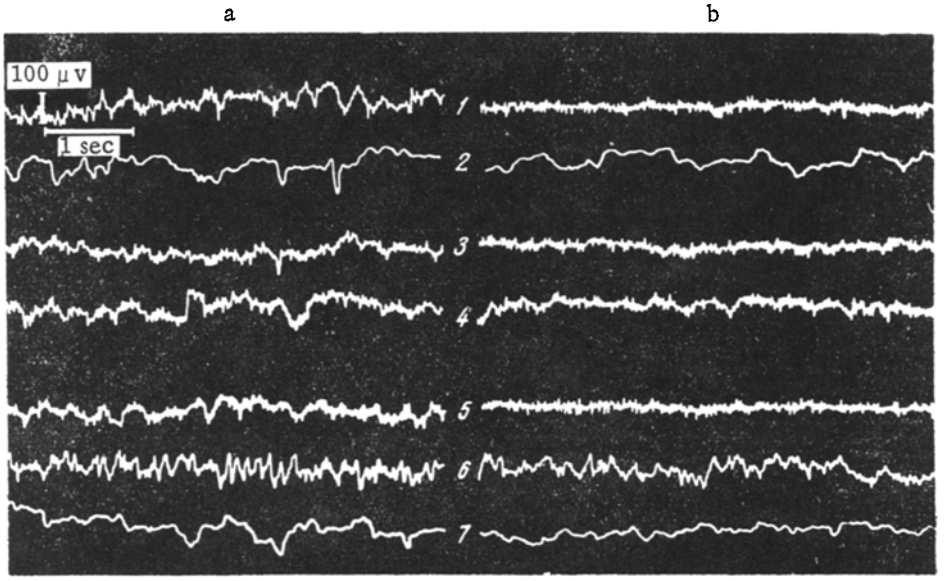

Fig. 3. Potentialization of Barbamyl's effect on the bioelectric activity of a rabbit's brain under the influence of Diazyl. a) EEG of cerebral cortex; b) EEG of optic thalami; 1, 3, 5) norm; 2) EEG taken 5 minutes after the intravenous injection of 35 mg/kg Barbamyl; 4) the same after 25 mg/kg Barbamyl; 6) EEG taken 5 minutes after the intravenous injection of 5 mg/kg Diazyl; 7) EEG taken 5 minutes after the intravenous administration of 25 mg/kg Barbamyl on a background of the action of the central cholinolytic Diazyl.

have a pronounced cholinolytic effect on the central cholinergic structures.

Although comparison of the effects of the various preparations shows some differences as to force, the differences were only found to be authentic in the case of Methyldifacyl and Methyldiazyl in relation to Difacyl and Diazyl, in the case of Aprophene, Pentaphene and Tropacine in relation to Difacyl, Diprophene and IÉM-268 and in the case of all these preparations in relation to the data of the control experiments.

These investigations of the potentializing influence exerted by central cholinolytics on the effects of hypnotics and anesthetics confirmed the rules demonstrated earlier regarding the link between structure and effect in a series of central cholinolytics. For example, there is a direct relationship between the increase in the central cholinolytic activity and the potentializing influence on hypnotic and anesthetic effects of preparations belonging to the Difacyl series as additional radicals are introduced into the structural formula. The transformation of Difacyl into Aprophene and Diazyl or of Diazyl and Difacyl into the β-methyl derivatives is a good example of this.

Therefore, on the basis of the experimental data obtained, one can conclude that preparations of the central cholinolytic group can potentialize the action of hypnotics and anesthetics. Central cholinolytics can be recommended for practical use in enhancing the effect of hypnotics and anesthetics (so that a smaller dose of the anesthetic is required to produce anesthesia of adequate depth).

SUMMARY

Methyldiazyl, Diazyl (benacthyzine), Aprophene, Pentaphene (Parpanit), Defacyl (Trasentine), Menthyldifacyl, Tropacine, Tiphen and thioester 22, preparations pertaining to the group of central cholynolytics, can potentialize the action of hypnotics and anesthetics (chloralhydrate), Barbamyl, Hexenal and thiopental). The enhanced action of hypnotics and anesthetics under the influence of the above complex esters is caused by the central cholinolytic properties of these preparations. There is a direct relationship between the degree of hypnotic potentialization and the intensity of the cholinolytic properties of these substances: The most potent central cholinolytics (Methyldiazyl, Diazyl, Pentaphene, Aprophene and Tropacine) have the strongest intensifying effect on hypnotic and anesthetic action.

Hence, central cholinolytics may be recommended for practical use in enhancing the action of hypnotics and anesthetics.

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