PERIPHERAL CHOLINOLYTIC ACTION OF SYDNOPHEN

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The Soviet preparation sydnophen is used in medical practice as a drug combining a psychostimulant action with moderate antidepressive activity [5, 6]. Sydnophen has been shown to have a central stimulating action, manifested as facilitation of conditioned reflexes, tactile and audiogenic hyperreflexia, and an activating action on the EEG [4]. Sydnophen potentiates the central effects of biogenic amines, probably because of its ability of inhibit monoamine oxidase activity [3]. During clinical use of sydnophen, it may have not only a central action, hut also an effect on peripheral parts of the nervous system.

The aim of this investigation was to study parasynpathetic peripheral chronotropic effects on the heart of anesthetized cats.

EXPERIMENTAL METHOD

The ECG, the cardiointervalogram, whose amplitude reflects the duration of the cardiac cycle [11], blood pressure (BP) and respiration rate were recorded in cats weighing 2-3 kg anesthetized with chloralose and pentobarbital (intraperitoneally, 60 and 10 mg/kg respectively), during electrical stimulation of the peripheral end of the divided vagus nerve in the neck (0.5-5 V, 10-40 Hz, 0.1-0.3 msec). The EEG also was recorded. Effects on the heart were calculated as the maximal change in the cardiac rhythm, relative to the initial cardiac rhythm (in %) [1]. After stable vagus effects had been obtained on the heart, sydnophen was injected into the jugular vein in doses of 0.002-20 mg/kg, and the magnitude of the parasympathetic effect was monitored for 15-60 min. During analysis of the dose-dependent curve, reduction of the vagus effect was determined (in % of the initial magnitude of the effect). To discover the significance of the difference between the initial responses of the heart and its responses after administration of sydnophen, nonparametric statistical tests were used [6], and confidence intervals were calculated by an express method [5].

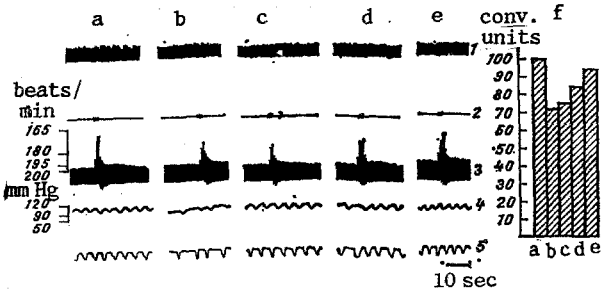

Fig. 1. Diminution of parasympathetic chronotropic effect on the heart after intravenous injection of sydnophen (2 mg/kg). a) Initial effect; b, c, d, e) effects 3, 8, 15, and 20 min after injection of sydnophen; f) graph showing parasympathetic effects on the heart. 1) ECG; 2) marker of stimulation of peripheral end of divided vagus nerve; 3) cardiointervalogram; 4) BP; 5) respiration.

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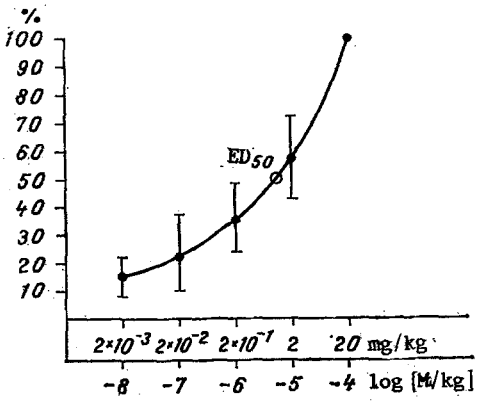

Fig. 2. Dose-dependent curve showing effect of intravenous injection of sydnophen on diminution of parasympathetic chronotropic effects on the heart. Ordinate, reduction of effect (in %).

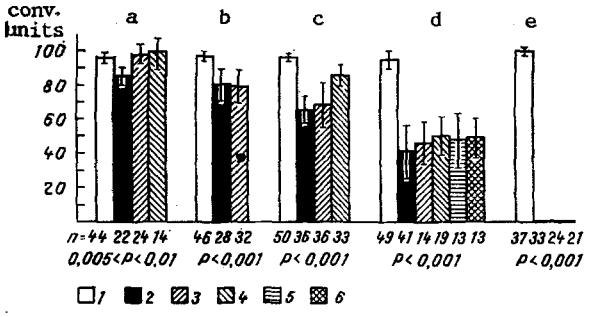

Fig. 3. Temporary development of reduction of parasympathetic chronotropic effect induced by different doses of sydnophen: a) 0.002 mg/kg, b) 0.02 mg/kg, c) 0.2 mg/kg, d) 2 mg/kg, e) 20 mg/kg. Ordinate, magnitude of effect (in conventional units). 1) Initial effect; 2) 1-3 min after injection; 3) 4-8 min, 4) 9-15 min, 5) 16-20 min or more after injection.

EXPERIMENTAL RESULTS

Injection of sydnophen in doses of 2-3 mg/kg was accompanied in anesthetized cats by a mild degree of activation of the EEG and by a brief (for 10-15 min) increase of BP and of the heart rate (HR), in agreement with data in the literature [3, 4].

Stimulation of the peripheral end of the vagus nerve (with the given stimulation parameters) gave rise to a reduction in palpitation which varied in each experiment not more than 10% (Fig. 1,a). Intravenous injection of sydnophen in the given doses was immediately accompanied by a decrease in the parasympathetic chronotropic effect (Fig. 1, b,c). After 30-90 minutes, reestablishment of the initial values of the effect was observed in a series of experiments.

The considerable individual differences in responses to sydnophen must be noted. In some cats injection of 2-3 mg/kg caused only a small decrease (by 25-30%) of the vagus effect, as is demonstrated in Fig. 1f, whereas in other animals injection of the same doses was accompanied by complete abolition of the effect, which was not restored for several hours. This individual character of the response to the drug also has been noted in the literature [6, 8, 10]. Diminution or total abolition of the vagus effect did not correlate with the small changes in HR and BP; it was observed also in animals in which administration of sydnophen did not lead to any quickening of the initial rhythm or to any increase in BP (Fig. 1). Blocking of the vagus effect also was found after repeated (5-6 h after the first injection) injection of sydnophen, which was accompanied as a rule by reduction of BP and HR.

The blocking action of sydnophen on chronotropic vagus effects was dose-dependent (Fig. 2). The initial effective dose was 0.002 mg/kg; a 50% reduction of the chronotropic vagus effect was observed with a dose of under 2 mg/kg of 10^{-5} M/kg.

Observation on the development of vagus effects during 1-20 min after injection of sydnophen showed that the maximal blocking action occurred during the first 1-3 min (Fig. 3). With the smallest dose (Fig. 3a) a statistically significant reduction of the effect was observed only during the first 1-3 min. After 4-8 min the effect was fully restored. When higher doses were used, both the slower development of the recovery process and a greater decrease of the vagus effect were observed (Fig. 3b-f). Injection of 20 mg/kg of sydnophen in all eight experiments led immediately to complete abolition of the chronotropic vagus effect (Fig. 3e). Only in three experiments was some degree of recovery of the effect observed to begin after 1.5-2 h.

Reduction of the vagus effect was not due to injection of an additional volume of fluid into the heart. Control injection of Ringer's solution, in which the sydnophen was dissolved, was never accompanied by eduction of the vagus effect. A tendency was actually observed for the effects to increase a little with the passage of time.

Thus together with its central stimulating action, sydnophen also has a peripheral blocking effect on the heart, evidence of its cholinolytic peripheral effect. It must be emphasized that this cholinolytic peripheral action is manifested over a wider range of doses, including at very low doses (0.002 mg/kg), which were not accompanied either by activation of the EEG or by changes in the initial levels of HR and BP.

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