caused inhibition of spontaneous APs and sharply inhibited (by 80-90%) the phasic response (Figs. 2c, d and 3). In a concentration of $1 \cdot 10^{-5}$M verapamil completely suppressed spontaneous and evoked APs and the phasic component of potassium contracture (Figs. 2d and 3).

The results of these investigations thus indicate that verapamil in very low concentrations ($1 \cdot 10^{-9}$-$1 \cdot 10^{-7}$M) selectively blocks the tonic component of potassium contracture of SMC of the portal vein; as a blocker of calcium channels, verapamil acts in higher concentrations ($1 \cdot 10^{-6}$-$1 \cdot 10^{-5}$M).

Since the present experiments showed that both the phasic and the tonic components of the potassium contracture disappeared completely in calcium-free Krebs' solution in the presence of 2 mM EDTA, this could evidently indicate that both these reactions depend on the inflow of extracellular calcium into the cell.

The fact that verapamil, in concentrations of $1 \cdot 10^{-9}$-$1 \cdot 10^{-7}$M, selectively inhibits the tonic components of potassium contracture, but that potassium membrane depolarization is preserved under these circumstances could indicate that verapamil has a specific effect on the coupling of excitation with contraction, by blocking the passive inflow of calcium into the cell. Only in higher concentrations ($1 \cdot 10^{-6}$-$1 \cdot 10^{-5}$M) does verapamil inhibit the phasic component of potassium contracture, by blocking the potential-dependent channels of the portal vein SMC membrane responsible for AP generation.

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ROLE OF VASCULAR THERMORECEPTORS IN THE MECHANISM OF COLD TREMOR INHIBITION BY OXOTREMORINE, DIAZEPAM, AND PHENTOLAMINE

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Experiments on cats showed that intravenous injection of oxotremorine, diazepam, and phentolamine not only inhibits cold tremor, but also reduces the flow of impulses from receptors of the subcutaneous veins. This decrease in the activity of the vascular thermoreceptors has been shown to be an additional component in the mechanism of the depriming action of oxotremorine and diazepam on cold tremor, whereas the decrease in thermoreceptor activity after administration of phentolamine is primary, and may perhaps be the dominant factor in the abolition of cold tremor.

KEY WORDS: cold tremor; thermoreceptors; neurotropic drugs.

Inhibition of cold tremor (CT) by certain neurotropic drugs is accompanied by an increase in the cutaneous blood flow, raising the skin temperature [3, 10, 11]. This fact suggests a definite role of the change in afferent flow from peripheral thermoreceptors in the mechanism of inhibition of CT by neurotropic drugs. The thermoreceptors of the subcutaneous and cutaneous vessels [4, 5], whose activity can be modified by central afferent influences and by the direct action of neurotropic drugs on smooth muscles, are particularly interesting from this point of view. These receptors, together with skin cold receptors, have been shown to participate in the regulation of CT [1, 2, 6].

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TABLE 1. Effect of Oxotremorine, Diazepam, and Phentolamine on Cold Tremor and Dynamics of Subcutaneous Temperature

Drug	Dose, mg/kg	Number of experiments	Abolition of cold tremor		Rise of subcutaneous temperature		
			number of experiments	latent period, sec	number of experiments	latent period, sec	amount of rise, °C
Oxotremorine	0,05	16	16	35,9±2,55	12	270,0±15,81	>2,0
Diazepam	0,5	16	16	29,3±2,91	10	242,0±41,65	3,9±0,74
Phentolamine	5,0	16	14	149,6±7,81	14	105,0±8,89	5,4±0,56

TABLE 2. Effect of Oxotremorine, Diazepam, and Phentolamine on Thermoreceptor Activity of Subcutaneous Vein

Drug	Dose, mg/kg	Activity of vascular thermoreceptors			
		number of experiments	discharge frequency before injection of drug, spikes/sec	number of experiments with reduced discharge frequency	maximum of decrease of discharge frequency after injection of drug, spikes/sec
Oxotremorine	0,05	16	23,3±1,03	12	14,5±0,91
Diazepam	0,5	16	24,7±1,77	10	11,9±0,78
Phentolamine	5,0	16	23,1±1,16	14	8,6±0,70

The object of the present investigation was to study the effect of oxotremorine, diazepam, and phentolamine on the activity of the vascular thermoreceptors and the possible role of the modified afferent flow in the mechanism of inhibition of CT by these drugs.

EXPERIMENTAL METHOD

Experiments were carried out on 48 cats anesthetized with chloralose and urethane (50 and 500 mg/kg respectively) after premedication with oxyphenonium bromide in a dose of 2.5 mg/kg. The anesthetized animal lay freely on its right side. CT was evoked by general cooling. Activity of the thermoreceptors of the subcutaneous veins in the region of the lateral surface of the thigh was recorded from the peripheral end of a divided cutaneous nerve. For this purpose a skin incision was made and the nerve isolated and its connections with the skin divided, leaving only vascular afferents. The skin outside the boundaries of the wound was raised with forceps and the resulting hollow was filled with mineral oil, under a layer of which the afferent activity was derived by bipolar electrodes. The electromyogram (EMG) of the sartorius muscle and activity traveling along the nerve fibers were recorded simultaneously on two channels of a Medicor electromyograph. Throughout the experiment parallel recordings were made of the rectal temperature and the subcutaneous body temperature of the foot of the left hind limb by means of thermocouples. The drugs for testing were injected through a cannula into the external jugular vein.

EXPERIMENTAL RESULTS

Injection of oxotremorine or diazepam into the shivering animal stopped the CT on average 30 sec after the injection, whereas the inhibitory action of phentolamine on CT developed after a longer latent period – on average after 2.5 min (Table 1). The inhibition of CT due to injection of these drugs in most experiments was accompanied by elevation of the subcutaneous temperature. After injection of oxotremorine and diazepam the rise of subcutaneous temperature developed long after the CT stopped. Conversely, injection of phentolamine led to an initial rise of subcutaneous temperature followed by inhibition of VT (Table 1).

Investigation of thermoreceptor activity of the subcutaneous veins showed correlation between the discharge frequency and the change in subcutaneous temperature. The gradual fall in the subcutaneous temperature caused by cooling was accompanied by a gradual increase in activity of the vascular thermoreceptors which, by the time of appearance of CT (subcutaneous temperature of the dorsum of the foot 26.6 ± 0.58°C), was about 23-25 spikes/sec. Injection of the various neurotropic drugs led in most experiments to a decrease in vascular receptor activity if under these circumstances the subcutaneous temperature rose (Table 2). The abolition of CT by oxotremorine and diazepam occurred when receptor activity of the subcutaneous veins had not yet changed (Figs. 1 and 2). The decrease in discharge frequency of the receptors began later, when these drugs were injected, and coincided in time with the rise of subcutaneous temperature. After injection of phentolamine the decrease in vascular thermoreceptor activity (coinciding in time with the rise of subcutaneous temperature) on the other hand, preceded the inhibition of CT (Fig. 3).

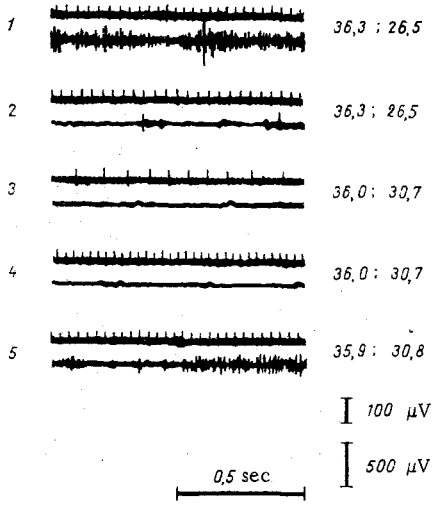

Fig. 1

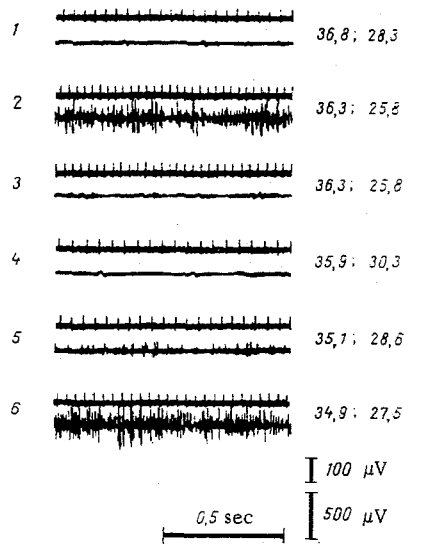

Fig. 2

Fig. 1. Effect of oxotremorine on vascular receptor activity and EMG of sartorius muscle during CT. 1) Before injection of oxotremorine; 2 and 3) 1 and 6 min respectively after injection of oxotremorine; 4 and 5) 30 sec and 3 min respectively after injection of scopolamine. Top beam records thermoreceptor discharge, bottom beam EMG of sartorius muscle. Numbers on right denote rectal and subcutaneous temperature (in °C) at times of recording.

Fig. 2. Effect of diazepam on vascular receptor activity and EMG of sartorius muscle during CT. 1) Before appearance of CT; 2) During CT and before injection of diazepan; 3, 4, 5, 6) 1, 5, 30, and 45 min respectively after injection of diazepam. Remainder of legend as in Fig. 1.

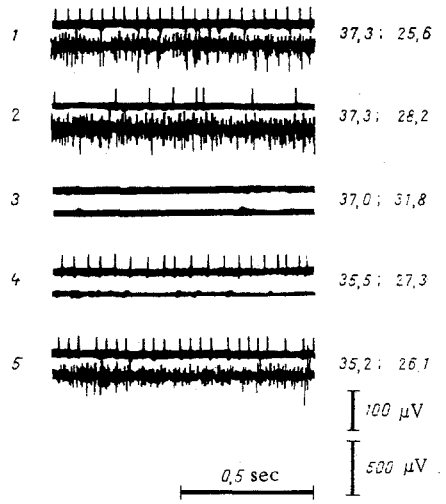

Fig. 3. Effect of phentolamine on vascular receptor activity and EMG of sartorius muscle during CT. 1) Before injection of phentolamine; 2, 3, 4, 5) 2, 7, 25, and 40 min respectively after injection of phentolamine. Remainder of legend as in Fig. 1.

The effect of oxotremorine after abolition of CT and elevation of the subcutaneous temperature (and the decrease in receptor activity) was not studied for a long time, but was terminated by injection of its central antagonist, scopolamine hydrobromide (0.5 mg/kg). Immediately after injection of the scopolamine marked thermoreceptor activity appeared, at a level higher than initially, and after 40-60 sec the tremor was resumed, whereas the skin temperature began to fall later – after 3-5 min.

Restoration of vascular thermoreceptor activity, when depressed by injection of diazepam and phentolamine (the greatest decrease was observed after 5-8 min) began gradually, after 12-18 min, and usually preceded or coincided with a gradual fall of subcutaneous temperature. Resumption of CT after injection of these drugs began later, after 30-50 min, in most experiments before the vascular thermoreceptor activity and subcutaneous temperature had returned to their initial level. This can evidently be explained on the grounds that at the moment of resumption of CT the body temperature was substantially reduced, and this most probably determined the new thresholds for onset of CT.

The results suggest that the decrease in discharge frequency of the vascular thermoreceptors may play a definite role in the mechanism of the inhibitory action of these neurotropic drugs on CT. The abolition of CT after injection of oxotremorine and diazepam must be assumed to be due to the direct action of these drugs on the central mechanism of regulation of CT; the subsequent decrease in vascular receptor activity is only an additional contributory factor. Changes in vascular thermoreceptor activity may be due to the exclusively inhibitory influence of oxytremorine on the central mechanisms controlling the cutaneous blood flow, for its peripheral effects were blocked by the preliminary injection of oxyphenonium. The effect of diazepam on the receptors, however, may depend not only on the central action of this drug, but also on its spasmolytic action on the vascular smooth muscle [7].

The effect of phentolamine, on the other hand, began with a reduction in vascular receptor activity on account of the marked peripheral α-adrenolytic action of this drug; for that reason the abolition of CT after injection of phentolamine is evidently the result of a reduction in the flow of information from the vascular thermoreceptors.

The depriming action of the neurotropic hypothermic drugs on CT may therefore be due both to their direct effect on the central mechanisms regulating this process and also to an indirect effect, through a decrease in the activity of the thermoreceptors conveying information about cold. It must be remembered that the decrease in vascular receptor activity after administration of neurotropic drugs does not arise in isolation, for it is connected in its causation with the tone of the subcutaneous and cutaneous vessels, and an increase in the cutaneous blood flow, raising the skin temperature, must inevitably lead to a decrease in the tonic activity of the specific cold receptors of the skin which, in their functional characteristics, correspond completely to the thermoreceptors of the subcutaneous veins [5, 8, 9].

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