ROLE OF AFFERENT IMPULSES IN THE MECHANISM OF AUTONOMIC RESPONSES TO ACONITINE AND VERATRINE

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After injection of aconitine and varatrine into the occipital artery supplying the ganglia nodosa of the vagus nerve with blood, vomiting and hypotensive responses develop. Interruption of the flow of afferent impulses (by division of the vago-sympathetic trunk or its blocking by procaine) prevents development of the vomiting reflex. In experiments on cats intraarterial injection of the alkaloids potentiated depressor responses to electrical stimulation of the central end of the vagus nerve.

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Our previous investigations [2, 3] showed that hiccup and vomiting movements in guinea pigs and vomiting movements in dogs arising through the resorptive action of aconitine and veratrine are due to the effect of these alkaloids on the ganglia nodosa of the vagus nerve. The mechanism of this effect is one of extreme intensification of the flow of spontaneous afferent impulses reaching the ganglia nodosa along the vagus nerve.

In the present investigation we studied changes in autonomic responses to electrical stimulation of the central end of the vagus nerve following injection of alkaloids directly into the ganglia nodosa.

EXPERIMENTAL METHOD

In consideration of some defects of methods of obtaining autonomic responses in dogs under chronic experimental conditions [4, 5], we developed a method of evoking vomiting in these animals by stimulating the vago-sympathetic trunk without exteriorizing it into a skin flap. For this purpose, bipolar platinum electrodes, interpolar distance 4-5 mm, were inserted into the vago-sympathetic trunk. The electrodes were insulated from surrounding tissues with polyethylene film. Wires soldered to the electrodes were brought out through a channel in the subcutaneous cellular tissue in the region of the back of the neck. The experiments began 3 days after the operation. The blood supply to the ganglion nodosum was first isolated, for which purpose small vessels in the region of bifurcation of the common carotid artery except the occipital and ascending pharyngeal arteries, were ligated. The common carotid artery was exteriorized in a skin flap in the middle third of the neck. Preliminary experiments showed that injection of aconitine (2 μg/kg) and veratrine (5 μg/kg) into the blood stream in the common carotid artery after isolation of the ganglion nodosum consistently produced vomiting in dogs with an intact vago-sympathetic trunk.

In one of the dogs the electrodes were inserted into the intact vago-sympathetic trunk, in another animal into the vago-sympathetic trunk above the segment exteriorized into the skin flap, and in a third dog into the vago-sympathetic trunk above the level of its division, carried out one year before the start of the experiments now described (in this dog intraarterial injection of the alkaloids in these and higher doses did not produce vomiting). The vomiting effect was recorded pneumographically by recording respiratory movements of the animals on the smoked drum of a kymograph.

In acute experiments on 20 cats under chloralose anesthesia (70-80 mg/kg, intravenously) the alkaloids were injected into the blood stream in the occipital artery supplying the ganglion nodosum. The vagus nerve on the side of injection was divided in the middle third of the neck. Stimulating electrodes were placed on the vagus nerve above the point of its division and above the ganglion nodosum. Square pulses were applied from a type IG-6 stimulator. The hypotensive and respiratory effects of electrical stimulation of the vagus nerve were recorded before and after injection of the alkaloids.

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Fig. 1. Vomiting response in dogs evoked by electrical stimulation and intraarterial injection of alkaloids. A) Electrical stimulation (T); B) combined action of veratrine (V) and electrical stimulation (T) against background of procaine blocking (N) of vago-sympathetic trunk; D) the same after division of vago-sympathetic trunk. Here and in Fig. 2, from top to bottom: arterial pressure, respiration, time marker (3 sec).

EXPERIMENTAL RESULTS

Experiments on Dogs. Stimulation of the vago-sympathetic trunk with pulses of adequate intensity evoked vomiting movements in all experimental dogs.

The vomiting reflex arising in response to stimulation was characterized by the almost complete absence of a latent period and by cessation of vomiting movements with the end of stimulation. When continuous stimulation was applied for 10 sec (35-40 V, 30-50 Hz, 0.1 msec), vomiting movements began from 1 to 1.5 sec after switching on the current. If a series of threshold stimuli were applied, the latent period was not increased (Fig. 1A). With a decrease in intensity of stimulation to 8-10 V, no vomiting effect developed.

Against the background of intraarterial injection of subthreshold doses of aconitine (1.5-1.7 μg/kg) and veratrine (3.0-3.5 μg/kg), subsequent stimulation of the vago-sympathetic trunk evoked vomiting movements, which continued long after the period of stimulation. These same experiments showed that after preliminary injection of the alkaloids the voltage required to evoke vomiting movements was much reduced (on the average by 8-10 V).

The time elapsing after injection of veratrine until electrical stimulation was 1-1.5 min, i.e., quite long enough for a possible emetic action of this dose of the alkaloid to be manifested. However, vomiting movements developed only if the current was switched on (Fig. 1B). If the vago-sympathetic trunk was stimulated above the point of procaine block (Fig. 1C) or division (Fig. 1D) against a background of intraarterial injection of the alkaloids, the vomiting effect appeared at once, even if subthreshold stimulation was used.

Experiments on Cats. This series of experiments was carried out in order to determine changes in the arterial pressure during electrical stimulation of the central end of the vagus nerve under the influence of intraarterial injection of aconitine and veratrine.

The character of change of the arterial pressure during electrical stimulation of the central end of the vagus nerve was determined by the intensity of stimulation. With stimulation of the order of 8-10 V or less, usually pressor responses developed. With an increase in strength of stimulation, the response changed to depressor, and with stimulation of the order of 20-22 V or above most responses were depressor (Fig. 2A).

This change in character of the vascular response with an increase in intensity of stimulation has been observed by other workers and attributed to gradual involvement of different groups of nerve fibers in the response. The hypotensive response to stimulation of greater intensity are attributed to excitation of nonmedullated afferent fibers belonging to group C [6, 9].

Fig. 2. Effect of aconitine on character of vascular responses to electrical stimulation of the vagus nerve. A) conversion of pressor response into depressor with increase in intensity of stimulation and increase in depressor against a background of aconitine administration (5 μg); B) injection of larger dose of aconitine (10 μg); C) inhibition of depressor response by aconitine (20 μg); D) distortion of pressor response by aconitine. Parameters of stimulation for A_1 and $D_{(1,2,3)}$ 10-12 V, 20 cps, 0.5 msec, 5 sec; for $A_{(2,3,4)}$ 20 V, 20 cps, 0.5 msec, 5 sec; for B, $C_{(1,2,3,4)}$ 20 V, 20 cps, 0.5 msec, 5 sec.

Intraarterial injection of aconitine and veratrine considerably potentiated the hypotensive effect of electrical stimulation. The minimal dose of aconitine causing an increase in the hypotensive effect of electrical stimulation of 15-20 mm Hg was 5 μg per animal (Fig. 2A). It was 6-7 times smaller than the minimal dose of this drug causing a decrease in arterial pressure when injected intravenously.

Injection of 10 μg aconitine potentiated the hypotension still further. Whereas the duration of the hypotensive response before injection of the alkaloid was limited to the period of stimulation, after injection of aconitine it was increased 3-4 times (Fig. 2B). With a further increase in the dose of aconitine (to 15-20 μg per animal, intraarterially) only transient potentiation of the hypotensive response to electrical stimulation took place, followed by inhibition of the hypotensive response. Between 5 and 10 min after injection of 20 μg aconitine, stimulation of the central end of the vagus nerve ceased to evoke a hypotensive response and apnea (Fig. 2C).

It is interesting to note that the effect of alkaloids on the vascular responses to electrical stimulation of the central end of the vagus nerve was limited to the region of the ganglion nodosum. Stimulation of the vagus nerve above the ganglion nodosum evoked the same response as before injection of the alkaloids.

It is clear from Fig. 2D, that injection of aconitine (10 μg per animal, intraarterially) led to distortion of the pressore response to electrical stimulation of the vagus nerve in the middle third of the neck. Stimulation of the vagus nerve above the ganglion nodosum, however, was accompanied as before by a pressor response. It can thus be concluded that if alkaloids are injected by our method, stimulation of the vasomotor centers does not take place, because injection of varatrine and KCl via the vertebral artery, supplying blood to the vasomotor centers, constantly evokes a hypotensive response, which we never found in our experiments. The results obtained confirm the views of S. V. Anichkov and co-workers [1] on the mechanism of the vomiting action of aconitine. It follows from the results of our experiments that after intraarterial injection of aconitine and veratrine the intensity of electrical stimulation of the vagus nerve evoking vomiting and hypotension is considerably reduced.

The results also show that impulses must be present in the vagus nerve before vomiting and a hypotensive effect can arise in response to intraarterial injection of the alkaloids. Interruption of the flow of impulses (by procaine block or division of the vagus nerve) leads to disappearance of the vomiting effect in response to injection of the alkaloids in doses much above threshold. Hence, a flow of impulses running to the centers, which could bring about these responses, does not arise in the ganglia nodosa of the vagus nerve under the influence of intraarterial injection of aconitine and veratrine, and consequently, they do not

possess receptors, stimulation of which, as some authors have suggested [7, 8], is responsible for the appearance of these autonomic responses.

On the basis of the results of the experiments just described and others performed previously it can be concluded that the mechanism of vomiting and hypotension evoked by aconitine and veratrine by their resorptive action is based on stimulation of peripheral receptors belonging to the vagus nerve system, with subsequent intensification of the flow of impulses reaching the region of the ganglia nodosa from them.

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