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CHARACTER OF BLOOD PRESSURE CHANGES UNDER THE COMBINED ACTION OF PRESSOR AND DEPRESSOR AGENTS

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During contact of an organism with the external environment, as a rule it is subjected to the action of several stimuli, which is realized through neurohumoral influences, including those on the heart and vessels. The resultant response of the hemodynamics under these conditions is the combined response of the hemodynamics under these conditions is the combined resonse of neurohumoral stimuli which differ in direction and in the mechanism of their action, and it is this which determined interest in the problem of the combined effect of these stimuli on the circulatory system [1, 3, 4]. Changes in arterial blood pressure (BP) in response to electrical stimulation of depressor and carotid nerves, leading to shifts in the opposite direction, have been demonstrated in the literature [4, 7]. A mainly depressor effect was exhibited, but its magnitude was less than that in response to separate application of these stimuli. Predominance of dilator responses of blood vessels of skeletal muscles and the small intestine was observed during simultaneous stimulation of the constrictor and dilator zones of the hypothalamus in cats [2, 6] and of the carotid and median nerves in dogs [1]. A similar effect also was obtained to the combined action of histimine and noradrenalin (NA) on vessels of the microcirculatory system in rats [5]. It is not yet clear what changes take place in BP as an integral parameter of the systemic hemodynamics in response to the combined action of two vasoactive substances with opposite effects.

The aim of this investigation was to study the character and magnitude of changes in the systemic BP in response to a combination of pairs of pressor and depressor substances, giving rise to opposite and equal effects on it: NA and angiotensinamide (ATA), and acetylcholine (ACH) and histamine (HA).

EXPERIMENTAL METHOD

Experiments were carried out on 27 male and female cats weighing 3-5 kg and anesthetized with urethane (1 g/kg), with the use of heparin (1500 U/kg), with an open chest and with artificial ventilation of the lungs. Changes in BP in response to combined intravenous injections of two vasoactive substances, opposite in their action but equal in the magnitude of their effect, were studied in the experiments. As pressor agents we used NA hydrotartrate (in a dose of 1-32 μg/kg) and ATA (0.25-10 μg/kg), and as the depressor agents — ACh chloride (0.0001-10 μg/kg) and HA dihydrochloride (0.25-8 μg/kg). Doses of the substances causing changes in BP by 25 ± 3, 50 ± 5, and 75 ± 10% relative to its initial level when injected intravenously and separately, determined in preliminary experiments, were used. These vasoactive substances were diluted in physiological saline so that their test doses were contained in a volume of solution equal to 0.5 ml. The preparations were injected into the animal's femoral vein. The systemic BP was measured in the left subclavian artery by means of a pressure indicator with mechanotron transducer (made by the experimental workshops of the Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR). The pressure

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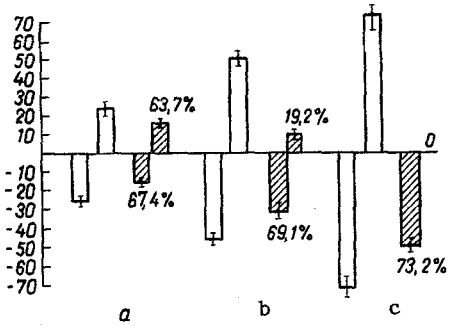

Fig. 1

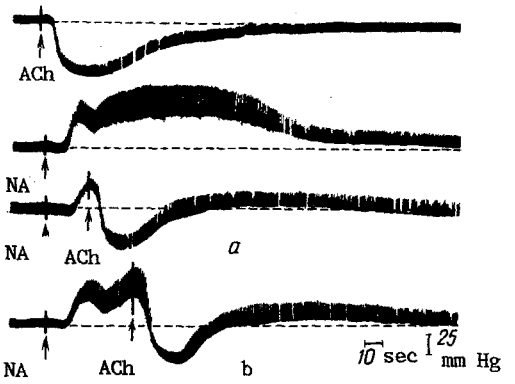

Fig. 2

Fig. 1. Changes in BP during simultaneous combined intravenous injection of NA and ACh. Ordinate, changes in BP (in % of initial level). a) Combined intravenous injection of NA and ACh in doses which, when injected separately, induced changes of BP by 25 ± 3% of initial level; b) the same, by 50 ± 5%; c) the same, by 75 ± 10%. Unshaded columns show values of effects on BP of separate intravenous injection of substances, shaded columns – in response to combined injections of substances; vertical lines indicate mean error of the means. Numbers give magnitudes of phases of combined response as a ratio, in per cent, of values of effects of separate injection of stimulus on BP.

Fig. 2. Changes in BP in response to intravenous injection of ACh preceded by action of NA. Two top curves show changes in BP in response to separate intravenous injection of ACh in a dose of 1 μg/kg and NA in a dose of 16 μg/kg. a) Intravenous injection of ACh during initial period of elevation of BP following injection of NA; b) time of reaching maximum of pressor response. Arrows indicate times of injection of substances. Calibration: 2.5 mm Hg, 1 sec.

was recorded on a N-327-5 high-speed automatic writer. The experimental results were subjected to statistical analysis by the Fisher–Student t test.

EXPERIMENTAL RESULTS

Combined simultaneous intravenous injection of NA and ACh in doses causing a change of BP by 25 ± 3% of its initial level when injected separately, induced biphasic changes in BP; a depressor response always developed initially, and this was followed by a pressor response. Values of the depressor and pressor phases were closely similar at 17.2 ± 1 and 16.1 ± 1% relative to the initial level, or 67.4 ± 1 and 63.7 ± 3% relative to the effects of the drugs separately (Fig. 1a).

When combinations of NA with ACh were used in doses which, separately, induced pressor and depressor effects on BP by 50 ± 5% of its initial value, just as in the previous case biphasic changes of BP were recorded, but the depressor phase was greater in magnitude and reached 32.9 ± 1% of the initial level, whereas the pressor phase was less – only 9.6 ± 1% of the initial level, which, when expressed as a ratio of the effects of the separate actions of these substances, was about the same value in the first case, namely 69.1 ± 2%, but much less in the second case – 19.2 ± 1% (Fig. 1b).

In the third trial, where combinations of agents were used in doses that when applied separately induced changes of BP by 75 ± 10% of initial value, the combined effect resulted in a monophasic reduction of BP by 49.4 ± 2% of initial level, which is 73.2 ± 3% relative to the value of the effects of separate application.

Frequently, with an increase in the intensity of a combination of stimuli with opposite effects, the depressor phase of the combined response exceeded in magnitude the pressor phase, or the latter was almost completely reduced. It was found that changes in BP were closely similar, both qualitatively and quantitatively, in response to all paired combinations of NA and ACh, NA and HA, ATA and ACh, and ATA and HA, regardless of the mechanisms of action of the vasoactive substances lying at the basis of the changes in BP.

Because depressor response for isolated application of vasoactive substances is shorter in the latent period (on average 8.6 ± 4 sec) compared to pressor response (14.7 ± 6 sec), we can assume that the change of BP for combined intravenous injection is not the result first and foremost of the length of the depressor phase. To clarify this we performed experiments in which ACh or HA in doses that when applied separately induced reduction of BP by 50 ± 5% of initial value were administered against a background of elevated BP induced by previous application of NA or ATA. Apparently, no matter if the depressor is introduced in the initial period of increasing BP in response to the action of the pressor (Fig. 2a) or at the moment when BP reaches the maximum (Fig. 2b), invariably the pressor response is replaced by the depressor, the magnitude of which on average is 32.3 ± 2% of the initial BP level. Therefore, the formation of the initial depressor phase of the total reponse in the combined intravenous application, in a different direction than the effect of the vasoactive substances, is independent of the difference in the latent period actions of the applied agents.

Thus a special physiological feature of the combined response of BP to paired combinations of stimuli with opposite effects but equal in magnitude (pressor and depressor vasoactive drugs) is a biphasic change in the systemic BP. The magnitude of this initial - (depressor) and also of the subsequent (pressor) phase of this response was less than the corresponding changes in BP in response to injection of these stimuli separately. The character of the response of BP was found not to depend either on the mechanisms of action of the vasoactive drugs on the cardiovascular system or on differences in the latent periods of action of these substances, but was connected only with stimulus intensity. Thus, in response to a combination of agents which, if injected separately, caused changes in BP of 25 ± 3% of its initial level, both depressor and subsequent pressor phases of the response were closely similar in magnitude. With an increase in stimulus intensity definite predominance of the depressor over the pressor phase in the combined response was observed, and this could amount to complete disappearance of the latter.

Thus predominance of depressor responses of BP over pressor responses with an increase in the intensity of stimuli with opposite effects is not only characteristic of reflex influences [1, 2, 6], but also is manifested during the combined action of pressor and depressor humoral agents on the hemodynamics.

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