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The influence of apomorphine on the cardiovascular reactions induced by stimulation of the vagus nerve in the rabbit

Wpływ apomorfiny na reakcje sercowo-naczyniowe wywołane drażnieniem nerwu błędnego u królika

Recently a model of central regulation of circulation has been created. Its structure includes neurones and centres organised in a longitudinal manner. Higher centres by descending junctions may modulate cardiovascular functions connected with the operation of lower centres located in the spinal bulb, spinal medulla. Many data indicate that dopamine plays a significant role in central regulation of circulation. Its increased values were confirmed in the animals with hypertension (1). Many studies point to a significant role of central dopaminergic mechanisms in the regulation of circulatory system and especially located within abdominal tegmentum. Electric stimulation of this region induces dopaminergic neurones and causes a considerable rise in arterial blood pressure exceeding 35 mm of Hg. Many studies indicate that dopamine within central nervous system influences cardiovascular system by means of dopaminergic receptor DA2, and to some degree through receptor DA1 (3, 4, 5). In other papers the researchers take note to peripheral effect of dopaminergic mechanism in regulation of blood pressure and the frequency of cardiac action. It is realised mainly by inhibition of catecholamines secretion from the sympathetic nerve endings and adrenal medulla (6). The reaction of vagus nerve in cardiovascular regulation has been known for a long time (7). Its action is realised by means of sensory cardiovascular fibres, the stimulation of which causes a significant decrease in blood pressure and cardiac action resulting from inhibition of adrenergic angiostenotic fibres and supplying the myocardium. The value of this decrease depends on the frequency and strength of the stimulus.

Apomorphine is a specific stimulator of dopaminergic receptors in the central nervous system. Central application of apomorphine causes depolarising response similar to the one which is caused by dopamine administration. Recently there have been few reports concerning the influence of apomorphine on the involuntary mechanisms of regulation of circulation (2, 9).

In our studies we decided to investigate some aspects of dopaminergic mechanisms contribution in the reflex regulation of circulation caused by stimulation of afferent vagus with the application of the increasing force of stimulus and unilateral and bilateral stimulation before and after administration of apomorphine. We wanted particularly to draw attention to the changes in the phenomena of facilitation and occlusion of cardiovascular reaction that may be induced by apomorphine in a widely understood cardiovascular centre.

MATERIAL AND METHOD

The experiments were carried out on 30 rabbits of both sexes, crossbreeds, with body weight 3-5 kg. The 20% solution of urethane was used for anaesthesia at a dose of 1.5 g/kg. The skin and subcutaneous tissue was cut along the central body line from the lower jaw bone to upper edge of sternum. After uncovering of the trachea, it was cut across along the lower edge of thyroid gland and the tracheotomic tube was inserted. Vagus nerves were prepared on both sides. In order to record the arterial pressure a tube filled with Ringer fluid with heparine was inserted into the ear middle artery lumen and it was connected with the electromagnetic converter of electric manometer. Mean arterial blood pressure and cardiac action were registered on the magnetic carrier of computer. For stimulation of central sections of vagus nerves platinum electrodes were used and they were connected to square wave oscillator. To prevent the nerves from drying off, they were submerged in warm paraffin oil. The temperatures of oil and of the animal were maintained at 37±0.5°C. When the initial actions had been finished the animals were administered 2500 units of heparine. The actual experiment was initiated after an hour. The intensity of stimulation was expressed by multiple threshold stimulation (T) and it was the repeated reaction of pressure drop equal to 1–4 mm Hg. Square wave pulses with the following parameters were used for stimulation: frequency – 5 cycles per second, time – 20 seconds, the width of individual impulse – 1 msec. The intervals between stimulation were equal to 5 minutes. Apomorphine at a dose of 0.5 mg/kg administered to auricular vein was used for stimulation of dopaminergic receptors.

RESULTS

During the first series of experiments the value of pressure drop reaction and the change in frequency of cardiac action during stimulation of central sections of the left and right vagus nerves subsequently and then simultaneously with stimuli of the increasing intensity from 1 to 6 T were tested. The sum of unilateral effects was compared with the value of effects obtained during simultaneous bilateral stimulation of vagus nerves. When the sum was smaller than the effect of simultaneous bilateral stimulation, it pointed to facilitating of the circulatory reaction, and when it was bigger – to its occlusion. During the second series of experiments these tests were repeated after administering of apomorphine and waiting for about 40 minutes until the destabilisation of circulatory parameters connected with administration of the preparation itself subsided. Admin-

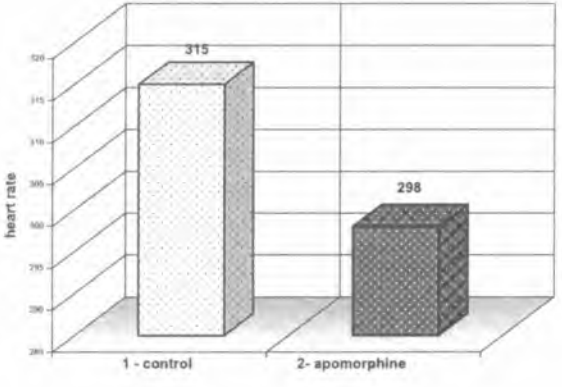

Fig. 1. Effect of apomorphine on initial heart rate

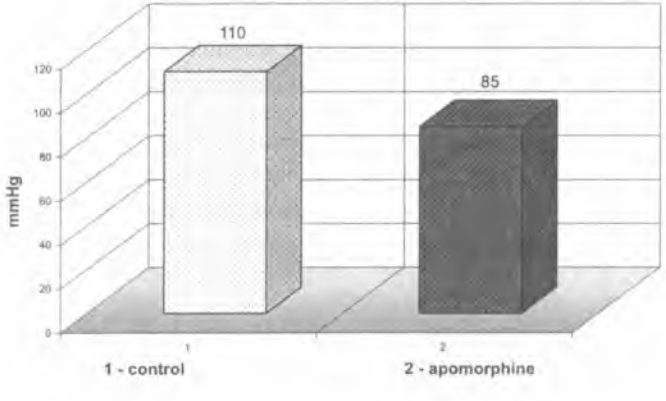

Fig. 2. Effect of apomorphine on initial arterial blood pressure

istration of apomorphine caused the drop of frequency of cardiac action on the average by 17±6 beats per minute. The results of such changes are shown in Figure 1.

Mean arterial pressure also got decreased by 15±7 mm Hg on the average (Fig. 2).

In the control group facilitation of pressure reaction was observed only with the lowest intensity of stimulation 1 - 1.5 T. When higher parameters of stimulating force were used, there was observed occlusion characterised by the domination of the sum of the unilateral effects value over the effect of simultaneous bilateral stimulation. This occlusion got intensified with the increase of stimulating force to the value of 4 – 5 T. For the value equal to 6 T it got progressed minimally. Administration of apomorphine caused that facilitation of pressure reaction was observed within the wider range of stimulation 1 – 2 T (Fig. 3). The observed changes in the values of the decrease in pressure after administration of apomorphine with application of identical stimulating parameters made us establish a new level of the reaction sensitivity. The change in threshold stimulation value was expressed in relative values with relation to the control conditions. In the group of animals after administration of apomorphine a highly significant increase in threshold stimulator value by 20.2% on the average was observed.

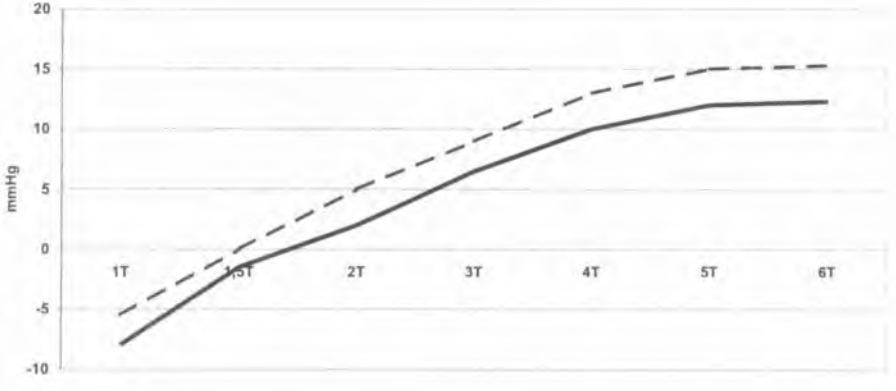

Fig. 3. Correlation between the size of area of active overlapping of the afferent innevation of the vagus nerves and the strength of the stimulus

Axis of abscissa - stimulation intensity, axis of ordinates - magnitude of the index determining the area of active overlapping of the innervation of both vagus nerves. Negative values of the index indicate facilitation, positive values indicate occlusion. After apomorphine administration facilitation of circulatory responses was observed at intensity of stimulation both 1-2 T.

DISCUSSION

The results of our experiments indicated the decrease in sensitivity of instinctive reaction both of its cardiac and vascular coefficients induced by stimulation of vagus nerves after administration of apomorphine. Each time the decrease in cardiac action and arterial blood pressure was observed and it was not so apparent with intraventricular administration. (5). Usually after intraventricular administration of apomorphine a decrease in arterial pressure with simultaneous increase in cardiac action frequency was observed (6). In our experiments we always observed the decrease in pressure and cardiac action frequency. These reactions were not present when prior to administration of apomorphine the non-specific dopamine blocker – haloperidol was used, which blocks both dopaminergic receptors DA1 and DA2. Experiments with application of selective dopaminergic blockers confirmed that apomorphine reacts in circulatory reactions mainly through receptors DA2 (3). Many authors think that apomorphine influences the circulatory system by reacting to dopaminergic receptors – DA2 receptors are stimulated independently of the dose and with relation to the receptor DA1 – it behaves like the antagonist or like agonist depending on the applied dose. It does not seem that in our experiments the effect of vasopresine increase was present during stimulation of vagus nerves. Such effect was observed by Hawthorn and co-workers (8) during the stimulation of vagus nerves in abdominal section. The phenomenon of facilitation of reactions occurring with low (1–2T) intensity of stimulation indicates that it is induced by the most excitable, low-threshold fibres of vagus nerve. Apomorphine slightly increases the scope of effect of stimulators at which the facilitation occurs in spite of the fact that absolute drops of pressure and cardiac reaction are slightly smaller than before its administration. The observed facilitation of pressure reaction after administration of apomorphine in a larger range of applied intensities of stimulation suggests that in widely understood cardiovascular centre apomorphine decreases overlapping of supraliminal zones of afferent stimulation with simultaneous increase in overlapping of subliminal stimulation for both in vagus nerves. These results point to the central mechanism of apomorphine reaction. The suggested data let us suggest those dopaminergic mechanisms play a significant role in the involuntary regulation of circulatory system by its central and peripheral reaction.

CONCLUSIONS

1. Apomorphine after peripheral administration decreases the initial values of cardiac action frequency and arterial blood pressure.

2. It decreases the reactivity of uncontrolled reaction induced by stimulation of vagal afferents through the increase of threshold stimulus value.

3. It increases the range of occurrence of facilitation reaction with small values of the applied intensities of stimulation indirectly pointing to its central reaction.

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STRESZCZENIE

Celem pracy było zbadanie wpływu apomorfiny na odruchowe reakcje krążeniowe związane z pobudzeniem nerwów błędnych u królika. Doświadczenia przeprowadzono na 30 królikach obu płci, mieszańcach w uśpieniu uretanowym. Drażniono dośrodkowe odcinki prawego, lewego i jednocześnie obu nerwów błędnych. Stosowane parametry drażnienia były następujące: częstotliwość 5c/sek., czas drażnienia 20 sek., szerokość pojedynczego impulsu 1 msek. Siłę drażnienia wyrażano wielokrotnością pobudzenia progowego

(1 T), za które uważano powtarzalny spadek ciśnienia, wynoszący 2 - 4 mm Hg. Odstępy pomiędzy drażnieniami wynosiły 5 min. Po dożylnym podaniu apomorfiny w dawce 0,5 mg/kg obserwowano spadek wyjściowych wartości ciśnienia tętniczego krwi o 15± 7 mm Hg, częstości akcji serca o 17±6 uderzeń na minutę. Po podaniu apomorfiny rozszerzeniu uległ zakres intensywności drażnienia, przy którym występuje zjawisko torowania reakcji krążeniowych. Zaobserwowane przez nas torowanie reakcji ciśnieniowej po podaniu apomorfiny w większym przedziale stosowanych intensywności drażnienia sugeruje, że w szeroko pojętym ośrodku naczyniowo–sercowym apomorfina zmniejsza zachodzenie na siebie stref nadprogowego aferentnego pobudzenia z jednoczesnym wzrostem zachodzenia stref podprogowego pobudzenia dla obu nerwów błędnych. Okluzja pojawiała się nieco później, po przekroczeniu wartości siły bodźca 2 T, i stopniowo narastała do 6 T. Efekt ten może być związany z ośrodkową stymulacją receptorów dopaminergicznych. Te dane wskazują, że mechanizmy dopaminergiczne biorą istotny udział w odruchowej regulacji krążenia, wywołanej drażnieniem aferentów błędnych.