THE EFFECT OF ANALGESIC AND NEUROPLEGIC AGENTS ON THE CORONARY CHEMOREFLEX

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It is known that certain substances, intravenously administered, can cause a reflex fall of blood pressure and bradycardia. These reflexes are evoked by stimulation of the receptors of the lungs and heart, and their afferent routes terminate in the body of the vagus nerves. Dawes and Comroe were the first to use the name "coronary chemoreflex" for the reflex from the cardiac receptors [14]. This reflex is caused by Veratrum alkaloids, serotonim, ATP, isourea derivatives, as well as by serum, plasma, and blood.* All these substances induce bradycardia and hypotension only when they enter the cardiac receptors, through the coronary vessels (the name of the reflex is related to this fact) [9,14].

The question of which cardiac receptors are responsible for the development of the coronary chemoreflex is still largely unsolved.

Veratrum alkaloids are known to induce the coronary chemoreflex by stimulating the cardiac mechanoreceptors [20]; according to the data of Mott and Peintal [18,21], serotonin stimulates a different type of cardiac receptor, and it is not yet clear which receptors react to serum, ATP, and isourea derivatives.

Our knowledge of the "coronary chemoreflex," therefore, cannot be considered complete from the physiological standpoint. Moreover, the existing data do not give sufficient basis for a more rational classification of the reflexes incorporated under this name.

The coronary chemoreflex is known to be one of the causes of hypotension in myocardial infraction, stenocardia, operations on the heart, and post-transfusion complications; it plays a substantial role in the action mechanism of certain medicinal preparations used to treat hypertonic conditions [12,14-16]. It has therefore become necessary to seek pharmacological agents which will influence the coronary chemoreflex.

We began our research in this direction with a study of the effect of analgesics, aminazine (chloropromazine), and reserpine on the coronary chemoreflex. The ability of these substances to alter the course of many viscero-visceral reflexes is generally known [2,8,17]. It therefore seemed wholly possible that they could affect the subject reflexes from the heart. Other important reasons for our choice of these substances were the extensive use of aminazine and analgesics in myocardial infarction, stenocardia, and operations on the heart and the attempts which have been made to use reserpine combined with veratrine to treat hypertonic conditions [1,15,16].

* Serum, plasma, and blood acquire the ability to induce coronary chemoreflex only after long storage (2-3 weeks).

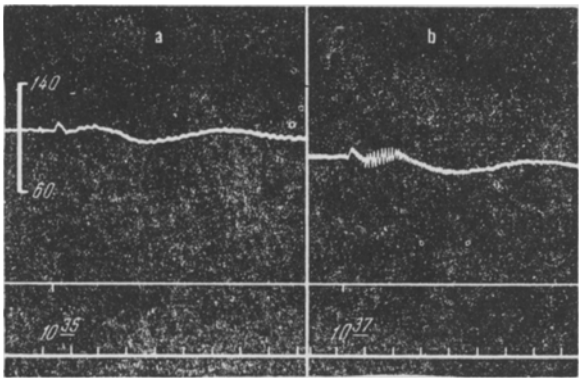

Fig. 1. Absence of bradycardia attending injection of 10 μg serotonin into the ascending aorta above the mouths of the coronary arteries (a) and pronounced reaction attending injection of the same dose into the cavity of the left ventricle (b). Curves show (top to bottom): arterial pressure and heart rhythm; indication of stimulation (serotonin injection); time (in 5-sec marks).

Experimental Methods and Results

The coronary chemoreflex was induced with the aid of veratrine and serotonin. The development of reflex bradycardia and hypotension from several reflexogenic zones attended the intravenous injections of these substances; serotonin was also observed to exert a direct effect on the vessels of both the pulmonary and the systemic circulation [12,13,19]. When the proper doses of veratrine and serotonin are introduced into the cavity of the left ventricle, the resulting bradycardia can be due only to stimulation of the cardiac receptors. This was shown by the experiments of Aviado [10] and Comroe et al. [12], in which veratrine and serotonin induced a definite reaction when they were introduced into the cavity of the left ventricle, but did not change the rate of the cardiac contractions when they were introduced, in the same doses, into the ascending aorta above the mouths of the coronary arteries.

After repeating the experiments of Aviado and Comroe, and obtaining the same results (Fig. 1), we decided to employ the method of injecting serotonin and veratrine into the cavity of the left ventricle in order to study the cardiac component of the coronary chemoreflex induced by these substances. This method also seemed entirely suitable for the study of veratrine hypotension. Serotonin, however, when injected into the cavity of the left ventricle, only induces the reflex from the heart. When used in doses which have a direct vasoconstrictor effect and lower the tonus of the vasoconstrictor centers. Therefore, the coronary chemoreflex is the essential, but not the only cause of the blood pressure reactions which develop when serotonin is injected into the cavity of the left ventricle.

We therefore used the data on the effect of analgesics, aminazine, and reserpine on these reactions solely for purposes of orientation. We paid particular attention to the portion of the hypotensive reaction which develops during the initial 10-15 min following the serotonin injection (in most cases, the coronary chemoreflex to serotonin develops and terminates within this period). Our final conclusions were based on experiments in which serotonin was injected into the lumen of the left coronary artery. As little as $\frac{1}{10}$ the amount of serotonin was required to produce the reflex from the heart* when the substance was injected into the lumen of the coronary artery, and this method of injection also prevented stimulation of the extracardial reflexogenic zones and any direct effect of serotonin on the vessels.

Experiments were performed on cats under urethan and urethan-chloralose anesthesia. Urethan was injected intravenously in a dose of 1.2 g/kg in the first case, and in a dose of 0.6 g/kg combined with 0.04 g/kg chloralose in the second. To permit the injection of veratrine and serotonin into the cavity of the left ventricle, small pieces of the III-IV ribs on the left were resected under conditions of artificial respiration. The left subclavian artery was dissected out and ligated at the level of the III rib; through an incision in the arterial wall, a metal cannula or polyethylene catheter was inserted, leading into the aorta and then into the cavity of the left ventricle.

At the same time, the animal was given an intravenous injection of heparin (100 units per kg). The catheter's position was visually controlled until the end of the experiment. The blood pressure was recorded in the common carotid artery by mercury manometer; the rate of the heart beat was determined along the recorded blood pressure curve. In several experiments, electrocardiographic observations were made with the aid of a

*When serotonin is introduced into the cavity of the left ventricle, the reflex from the heart is only induced by the amount of the substance which enters the lumen of the coronary vessels with the blood, i.e., approximately one-tenth of the amount injected.

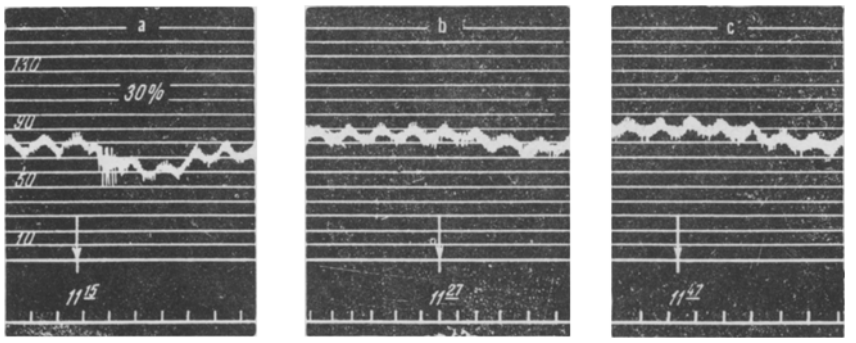

Fig. 2. Aminazine inhibition of the reflex reaction induced by the injection of 2 μg serotonin into the left coronary artery (↓): a) reflex reaction before injection of 1.5 mg/kg aminazine; b) 5 min after injection; c) 25 min after injection. Curves show (top to bottom): arterial pressure and heart rhythm; time (in 5-sec marks).

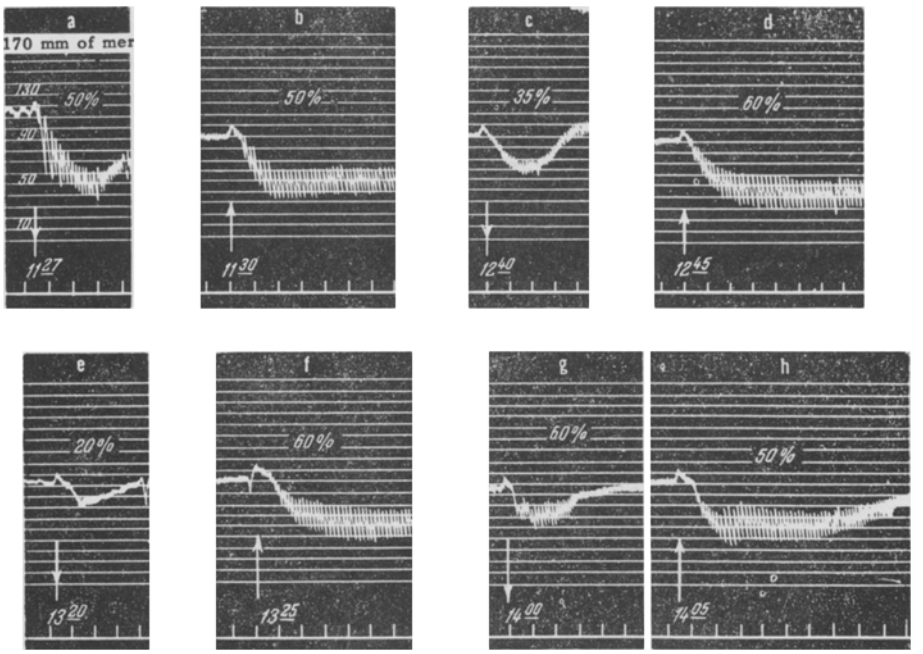

Fig. 3. Effect of reserpine on the reactions induced by the injection into the cavity of the left ventricle of 10 μg veratrine (↑) and 10 μg serotonin (↓): a) reaction to serotonin before reserpine injection; b) reaction to veratrine before reserpine injection; c) reaction to serotonin 1 hr after injection of 0.4 mg/kg reserpine; d) reaction to veratrine 1 hr 5 min after reserpine injection; e) reaction to serotonin 1 hr 40 min after reserpine injection; f) reaction to veratrine 1 hr 45 min after reserpine injection; g) reaction to serotonin 2 hr 15 min after reserpine injection; h) reaction to veratrine 2 hr 20 min after reserpine injection.

screened cathode-ray cardiograph. Veratrine was used in doses of 10-50 μg, serotonin in doses of 10-20 μg. To prepare for the injection of serotonin into the lumen of the left coronary artery, a catheter was inserted, as in Dawes's experiments, in the mouth of this artery from the lumen of the ascending aorta [13]. Dawes supplied the coronary artery with blood by connecting the free end of the catheter with the common carotide artery. In our experiments, blood was fed into the mouth of the left coronary artery from the femoral artery with the aid of a perfusion pump. This method, first used by N. V. Kaverina [3] to study the tonus of the coronary vessels, enabled us to create optimal conditions of myocardial blood supply. Serotonin was introduced in a dose of 1-2 μg

into a rubber tube which connected the pump with the catheter inserted into the mouth of the coronary artery. To avoid tachyphylaxis, veratrine was injected at half-hour intervals in all the experiments; serotonin, at 15-min intervals. Under these conditions, we managed to obtain at least three or four reactions of identical value.

In our study of the cardiac component of the coronary chemoreflex, the value of the reaction was estimated according to the decrease in the rate of the heart beat, expressed in percent of the original rhythm. The electrocardiographic data showed that the bradycardia observed was sinus in character.

The value of the depressor reactions was determined each time in percent of the blood pressure level before the reaction, and compared with the value of the original reaction, computed in the same manner. The analgesic and neuroplegic substances were injected intravenously.

The experiments showed that the reflexes to veratrine and serotonin changed identically under the influence of analgesics. The character and degree of the effect depended entirely on the dose of the analgesic. For example, morphine and promedole (4-phenyl-4-propoxy-1,2,5-trimethyl-piperidine hydrochloride) in doses of 1-2 mg/kg, and phenadone (methadone) in doses of 0.5-1 mg/kg did not, in most of the experiments, affect the reflex bradycardia. The reflex hypotension became either depressed or considerably intensified.

When the doses of morphine and promedole were increased to 4 mg/kg, and the phenadone doses to 2 mg/kg, the considerable decrease, or complete disappearance of reflex bradycardia and hypotension was observed in all the experiments. Restoration of the reactions, however, occurred as early as the 20th-30th minute, and the reflex bradycardia then observed often exceeded the original.

When aminazine was injected in a dose of 1-2 mg/kg, acute and sometimes total inhibition of the coronary chemoreflex was observed (Fig. 2). No restoration was, as a rule, observed for 2-3 hr. There is no parallel between the ability of aminazine to inhibit the coronary chemoreflex and the hypotensive effect of the drug: the reflexes were often totally inhibited, while the pressure remained high; in several cases, the inhibited reflexes were restored although the arterial pressure remained depressed.

Reserpine in doses of 0.3-0.5 mg/kg inhibited the reflex reactions to serotonin.

In a majority of experiments, inhibition of the reflex bradycardia and hypotension was observed as soon as 30 min after the reserpine injection, and the reactions remained inhibited for 2-3 hr. Occasionally, the reactions were inhibited 50-60%, and their restoration began after 2-2½ hr. The coronary chemoreflex to veratrine did not change stably under the influence of the same doses of reserpine: bradycardia could either increase or be inhibited; the depressor reaction usually did not change. In cases where veratrine and serotonin were both injected in one experiment, we noted a definite relationship between the effect of reserpine on the veratrine reflexes and the degree to which the reflexes to serotonin were inhibited. In the experiments in which reserpine inhibition of the reflexes to serotonin was only mildly expressed, we observed the reflexes to veratrine to be stronger. When the reaction to serotonin was completely suppressed, the reflex to veratrine was inhibited (Fig. 3).

Under the influence of analgesics, therefore, the chemoreflexes to serotonin and veratrine changed slightly. They became briefly inhibited only when morphine, promedole, and phenadone were used in amounts which notably deteriorate pulmonary ventilation, according to the literature data [4,6,7]. Aminazine induced inhibition of the reflexes in a dose of only 1-2 mg/kg. Doses several times larger than these are easily tolerated by the experimental animals [5,11]. Further experiments demonstrated that the effects of aminazine and the analgesics on reflex bradycardia induced by the injection of long-stored serum into the cavity of the left ventricle* followed the same characteristic courses already described.

It is probable that these substances have the same characteristic effects on all the reflex reactions lumped together under the term "coronary chemoreflex," and possible that this is also true in respect to the reflexes induced by the action of mechanical stimuli on the pressoreceptors of the ventricles and auricles. The data concerning the effect of reserpine on the coronary chemoreflex is, in our opinion, of particular interest. The question of why reserpine affects "veratrine" and "serotonin" reflexes differently must be investigated.

* In these experiments, as in all the preceding ones, the bradycardia developed solely as a result of stimulation of the cardiac receptors.

SUMMARY

Coronary reflex was induced with serotonin, veratrine, and serum. All these substances were administered to anesthetized cats into the cavity of the left ventricle or the left coronary artery. As shown, the analgesics (morphine, promedole, and phenadone) failed to produce any distinct effect upon the coronary chemoreflex. Low doses of aminazine (chlorpromazine) distinctly depressed the reflex. Reserpine depresses the reflex evoked by the administration of serotonin. The reflex in response to veratrine may be either intensified or inhibited.

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