HEMODYNAMIC CHARACTERISTICS OF POLYPEPTIDE SUBSTANCE P COMPARED WITH BRADYKININ AND PROSTAGLANDIN E_1

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The polypeptide called substance P (SP) belongs to a group of substances with high physiological activity. It has been ascribed the function of one of the neuromediators. Less attention has been paid to the vasomotor properties of SP, although some authors have stated that it has a probable role in the regulation of the systemic hemodynamics and of vascular permeability [2, 3, 6]. A preparation of SB was synthesized by M. Binnert at the Institute for the Study of Physiologically Active Substances, Berlin, East Germany.

In this investigation the effect of SP on the systemic circulation was studied in rabbits and rats, taking into account the metabolic function of the lungs in relation to physiologically active substances present in the body.

EXPERIMENTAL METHOD

Experiments were carried out on 35 rats weighing 220 ± 20 g and 16 rabbits weighing 3.0 ± 0.3 kg, anesthetized with urethane. Substances dissolved in physiological saline were injected in one stage; in a dose of 0.1-0.3 ml into the femoral vein of the rats, and in a dose of 0.5 ml into the right or left ventricle of the rabbits. Cardiac catheters with a bore of 0.8 mm were introduced into the rabbits through the jugular vein or carotid artery, with the chest closed and with the animal breathing naturally. Blood pressure in the femoral artery of the rabbits and in the carotid artery of the rats was recorded by means of a "Galileo" electromanometer.

Bradykinin triacetate (from Reanal, Hungary) and prostaglandin E_1 (PGE_1) (from Serva, West Germany) were used. Working solutions were made up on the day of the experiment. Each injection of the substance was given when the blood pressure was close to its initial level (100-110 mm Hg), at intervals of 5-7 min.

EXPERIMENTAL RESULTS

The results (Fig. 1) show that of the three substances chosen, SP had the greatest hypotensive activity, similar from the concentration point of view to that of PGE_1. Bradykinin activity, expressed per molar concentration, was three orders of magnitude lower. SP was used in the experiment in concentrations of 5 to 60 picomoles/kg. Larger doses of SP produced irreversible changes in blood pressure, or changes which took a long time to recover. Unlike bradykinin, SP caused no marked changes in diastolic pressure. As Fig. 1 shows, the range of effective concentration for SP was much wider than for bradykinin and PGE_1. Since both substances are known to be broken down intensively in the lungs [1], this fact can be attributed not only to differences in the reactivity of the structures of the vascular system, but also to differences in the degree of transformation of SP, bradykinin, and PGE_1, in the lungs, and, consequently, differences in the orientation of their physiological action.

In the next series of experiments, responses were compared when the substances were administered to rabbits "before the lungs" or "after the lungs," i.e., into the right or left

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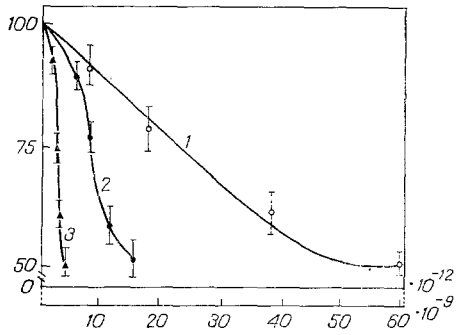

Fig. 1. Dependence of pressor responses on concentration for substance P (1), prostaglandin E_1 (2), and bradykinin (3). Abscissa, concentration of preparation (in 10^{-12} M; for bradykinin, in 10^{-9} M); ordinate, lowering of blood pressure (in %).

ventricle of the heart. The results were assessed as the dose of the substance which caused a standard hypotensive response; a fall in systolic pressure by 25 ± 5 mm Hg. The results showed that when SP was used in doses of between 10 and 35 ng/kg practically no difference was observed in the depressor responses when the drug was given by the two different methods. For bradykinin such a difference was found when doses of 0.5 ± 0.09 µg/kg were given to the right ventricle and 0.1 ± 0.014 µg/kg into the left ventricle. The greatest difference (22 times) was observed for PGE_1 in doses of 270 ± 30.1 and 13.5 ± 1.1 ng/kg, respectively.

By contrast with bradykinin and PGE_1, and also with serotonin, acetylcholine, and noradrenalin [1, 3], SP does not undergo any marked inactivation in the pulmonary circulation. Inactivation of SP is known to take place mainly in the liver [4]. Series of investigations conducted with the synthesized preparation of SP yielded information on its vasoactive action. So far SP has been regarded mainly as a substance with neurotropic action and its effect on the hemodynamics, including the microcirculation, has received little attention. The high biological activity of SP, its ability to pass freely through the pulmonary blood vessels, and to remain for a long time in the circulation, all suggest that SP may play an important role in the physiological regulation of the circulation. The doses used in the present experiments were completely comparable with quantities of SP detected in the blood by radioimmune methods [5].

The intensive destruction of bradykinin and PGE_1 in the pulmonary circulation, discovered previously and confirmed by the present investigations, deserves special attention. The lungs evidently play an important role in the control of physiologically active substances circulating in the blood stream and in the regulation of their local or generalized action.

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