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Symposium on substance P

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SIMPOZIJUM
O
SUPSTANCIJI P

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ANU BiH
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SARAJEVO
1961

B. PERNOW

SOME EFFECTS OF SUBSTANCE P IN MAN

In the original report by Euler and Gaddum (1931) SP was defined as a smooth muscle stimulating and blood pressure depressor factor, and we know now that these two effects are also obtained with the more purified preparations, the one containing 3,000 units per mg (Pernow, 1953) and now the chemically pure one, containing 30,000 units per mg (Franz, Boissonnas and Stürmer, 1961). Both effects are also observed in man following intravenous administration of SP and the present paper deals with some observations on the actions of SP on circulation and the intestinal muscles.

I. EFFECTS ON THE CIRCULATION

The typical response following intravenous administration of SP is a rapid fall in blood pressure. This effect, which is not blocked by either atropine, antihistaminics or ganglionic blocking agents, is obtained in all mammals and is due mainly to a peripheral vasodilatation (Euler and Gaddum, 1931; Euler, 1936). In the isolated rabbit ear Holton and Holton (1952) observed a vasodilatation following intraarterial administration of SP.

In the first study on the effect of SP in man (Liljedahl, Mattsson and Pernow, 1958) an immediate rise in pulse rate and fall in arterial blood pressure was observed following intravenous infusion of SP. A bright red flush in the face was noticed as a characteristic effect. All subjects felt throbbing sensations in their head. All reactions were transient and disappeared even during continued infusion. It was then possible to increase the infusion rate three to four times without any further reactions.

In order to study this preliminary observation more in detail the effect of SP on the central hemodynamics, splanchnic and forearm blood flow was studied separately. The SP preparation used had an activity of 550 Euler units per mg. It was dissolved in saline and given intravenously in amounts of 0.2—1.2 U./kg/min.

A. General symptoms

Immediately after starting the infusion the subjects felt warmth in their head and temporal pulsations. Simultaneously a bright red flushing was observed in the face, neck and arms. These symptoms

reached a maximum 1—2 min. after the start of infusion, lasted another 2 min. and then slowly disappeared in spite of a constant infusion rate. In some cases the symptoms returned, but usually to a milder degree, when the infusion rate was increased. In others the infusion rate could, after a few min., be increased manyfolds without any further symptoms. No further reactions were observed.

B. Effect on central circulation

(Dunér and Pernow, 1959)

Methods

These effects were studied in connection to heart catheterizations in healthy male volunteers. A double lumen Cournand catheter was inserted into the right heart from a cubital vein. A polyethylene catheter was put percutaneously into a brachial artery. Pressure recordings were obtained from the right ventricle, pulmonary artery, pulmonary arterial wedged position (PCV) and the brachial artery. Cardiac output was determined by the direct Fick's method, that is on ground of the oxygen uptake in the lungs and the difference in oxygen between arterial and mixed venous blood. Expired air was collected in Douglas bags. Blood oxygen content and capacity were analyzed spectrophotometrically.

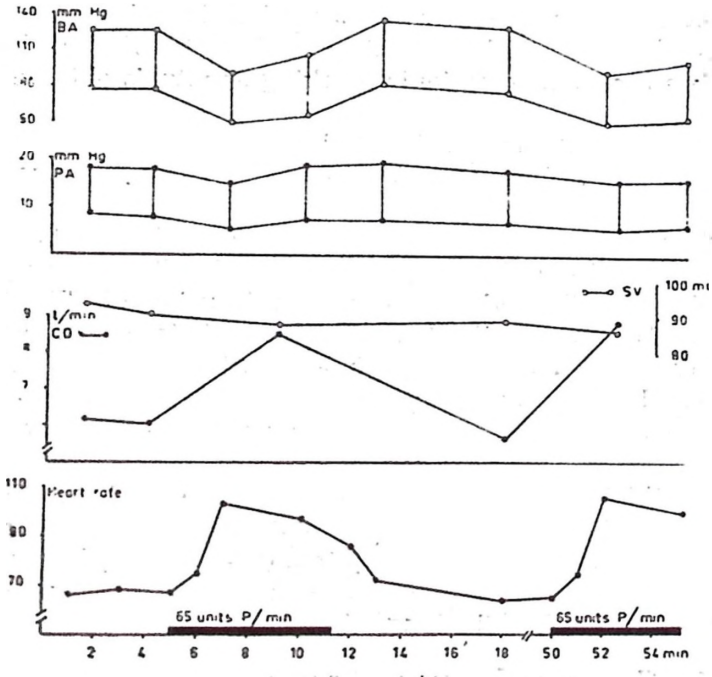


FIG. 1

Effect of repeated intravenous infusions of substance P on the central hemodynamics in man. BA = brachial artery, PA = pulmonary artery, CO = cardiac output, SV = stroke volume (Dunér and Pernow).

Results

Heart rate. — The heart rate immediately increased during infusion of SP in doses of 0.3 U./kg/min. or higher. The tachycardia was maxi-

mal 2 min. after the start of infusion. Normal pulse rate was resumed 1—2 min. after stopping the infusion.

Blood pressure. — Right ventricular, pulmonary artery and PCV pressures did not change significantly during SP infusion. The brachial artery pressure, however, dropped immediately after the start of infusion. Minimal values were recorded within 2 min., after which the arterial pressure again increased even during continued infusion. When the infusion was repeated 15—30 min. later, the same fall in arterial pressure, as well as in heart rate was, however, observed.

Oxygen uptake. — No change was observed in pulmonary oxygen uptake during SP infusion.

AV-O_2 difference. — During SP infusion the total arterio-venous oxygen difference, as calculated from brachial and pulmonary artery blood, decreased slightly.

Cardiac output and stroke volume. — At an infusion rate of 0.4 U./kg/min. and more the cardiac output increased slightly in all cases. This increase was entirely due to the increased heart rate since the stroke volume was usually formed unchanged during the infusion.

C. Effects on splanchnic blood flow

(in collaboration with Castenfors, Eliasch and Hultman)

Method

The method used was the dye clearance technique introduced by Bradley. Bromsulphalein was used as a dye, which is known to be exclusively eliminated by the liver. The dye was given in a constant i. v. infusion. It is known that the rate at which the liver can remove the dye is proportional to the concentration. When the rate of removal becomes equal to the rate of infusion, the blood level stabilizes, and, therefore, the rate of removal can be determined indirectly by measuring the rate of infusion. If the rate of removal and the proportion of dye removed by the liver from each milliliter of blood is known, the blood flow is simply determined by the relation

$$\text{blood flow} = \frac{\text{amount removed per min.}}{\text{amount removed from each ml of blood.}}$$

The technique therefore necessitates catheters in an artery and a hepatic vein. The assumptions of this clearance technique are that the liver solely removes the dye, and that the concentration of the dye obtained by catheter from the hepatic vein is representative of all of the blood leaving the liver.

Results

I. v. infusion of SP gave rise to a slight increase in splanchnic blood flow which was raised from 1,540 to 1,830 ml per min. Simultaneously the concentration of bromsulphalein increased slightly in both

arterial and hepatic venous blood at unchanged infusion rate, indicating a decrease in removal of dye by the liver. The explanation of this is not known but might suggest a shunting of dye through arterio-venous anastomoses in the liver.

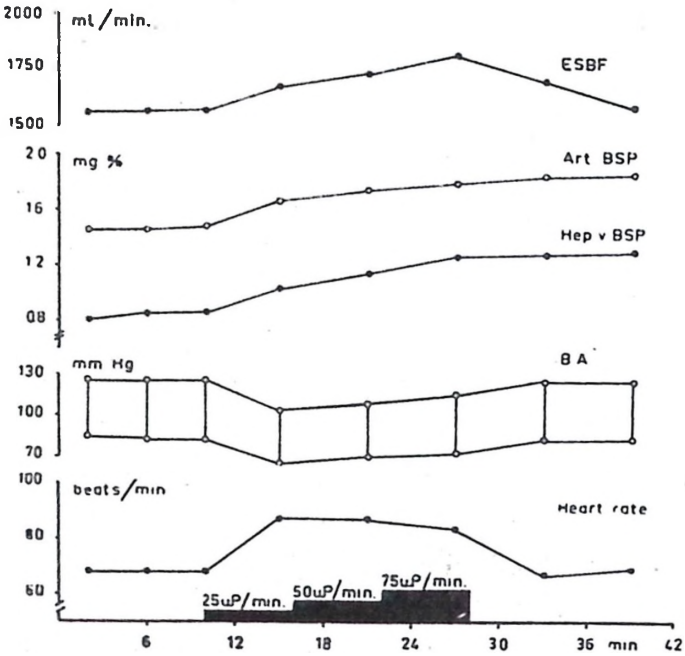


FIG. 2

Effect of intravenous infusion of substance P on the heart rate, brachial artery pressure (BA), bromsulphalein concentration of the brachial artery (Art. BSP) and hepatic vein (Hep. v. BSP) and the estimated splanchnic blood flow (ESBF) (Castenfors, Eliasch, Hultman and Pernow)

D. Effect on the blood flow of the forearm

(in collaboration with Wahren)

Method

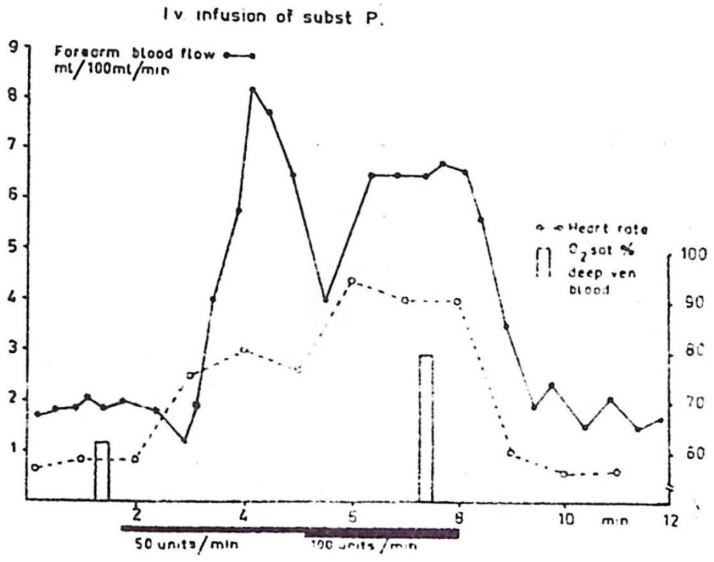
The observations were made on healthy male subjects lying in supine position. Forearm blood flow was measured by venous occlusion plethysmography as described by Graf and Westergren (1959). A polyethylene catheter was inserted percutaneously in a cubital vein and put about 8 cm in the distal direction into a deep vein, which is known to give practically pure muscle blood.

Result

After a latency of about 2 min. the usual increase was obtained in heart rate. The typical bright red flush was observed in the face, neck and arms. The forearm blood flow increased rapidly to maximum five times the resting level. A significant rise in oxygen saturation of the deep venous blood was obtained, indicating an increase in muscular blood flow, since the oxygen uptake of the muscle was supposed to be unchanged (Fig. 3).

FIG. 3

Effect of intravenous infusion of substance P on the forearm blood flow, the oxygen saturation of deep venous blood of the forearm and the heart rate (Pernow and Wahren).



Conclusions

Intravenous infusions of partly purified SP preparations were shown to elicit significant effects on the circulation in man. The predominant effect seems to be a peripheral vasodilatation with a fall in arterial blood pressure. An increased blood flow was observed specially in the muscles and skin, while the splanchnic blood flow was only moderately raised. The dilatation of the skin vessels caused a flushing which was best observed in the head and arms. Cardiac output was increased due to a raised heart rate, whereas the stroke volume was unchanged. The tachycardia was probably due to the rapid fall in blood pressure.

II. THE EFFECT ON THE INTESTINAL MOTILITY (Liljedahl, Mattsson and Pernow, 1958).

The most striking effect of SP is its stimulating effect on smooth muscle, specially that of the intestinal wall. This has been shown both on isolated segments and intestine »in situ«.

1. Studies on isolated segments of human intestine. Pieces of gut were obtained at operations and were, immediately after removal, placed in Tyrode's solution and, later on, suspended in an ordinary intestinal bath. Both duodenal, jejunal, and ileal segments were found to be sensitive to SP, the duodenum however about 4—5 times less sensitive than the other segments mentioned. In the ileum preparations 0.3 units per ml bath fluid produced a contraction about twice the spontaneous amplitude.

The action of SP consisted in an initial relaxation, rapidly followed by a gradual increase in tone. Small concentrations of SP usually pro-

duced an increase in the spontaneous movements only, while larger amounts gave rise to an increased tone. The slow-reacting type of contraction, typical for SP on all smooth muscle organs, is quite distinguishable from the rapid response produced for instance by ACh.

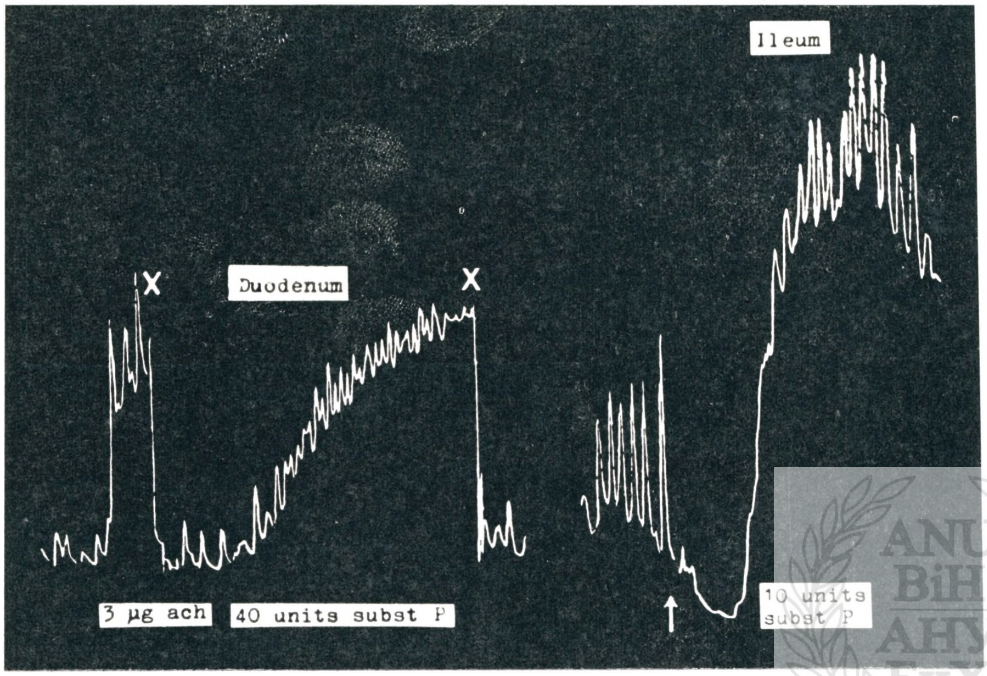


FIG. 4

Effect of substance P and acetylcholine on the isolated human, duodenum and ileum. Bath volume, 15 ml. At X, changing of the bath fluid (Liljedahl, Mattsson and Pernow).

2. Effect of intravenous infusion of SP on intestine »in situ« (illustrated by a film). The radiographic recordings were performed with a cinecamera, type Arriflex (35 mm film) connected to a Philips image amplifier. The camera speed was constantly 16 frames per second. To obtain constant exposure of the film during the whole examination, independently of the varying object thickness, amount of contrast media etc., a millivoltmeter was connected to the intensifier. By this device the amount of light emanating from the intensifier could be evaluated directly and the X-ray intensity be adjusted accordingly. The recordings were, as a rule, made in consecutive periods of 10—15 seconds. Screen examinations were made in the meantime in short periods and at low X-ray intensity.

Intravenous infusions of 1—1.5 mg of SP (600—1,000 units) during 20-min. periods elicited within 5 min. an increase in intestinal motility. This change was demonstrable for both the segmental and the peristaltic movements. In the fluoroscopic picture local deep constrictions of the intestinal lumen predominated, which indicated powerful con-

tractions of the circular muscles. In some areas the intestinal lumen diminished markedly, which suggested a general rise in tone of the intestinal muscles. Now and then powerful, prolonged peristaltic waves were seen, which forced the barium content of the intestine in the anal direction. The increased motility was observable during the whole period of infusion, and for 10—20 min. after the end of infusion.

In a case of intestinal paralysis the gut was initially enormously distended and showed no types of movements. The patient then got 1,000 units SP during a 20-min. infusion. Eight minutes after the start of infusion a few segmental contractions rapidly changed the shape of the intestine, and were followed by adequate peristaltic waves extended over about 10—20 cm of the intestine in an aboral direction. This activity, however, became fainter, even during continuous infusion, and disappeared rapidly after the end of infusion.

Summary

Highly purified substance P preparations were infused intravenously in healthy human subjects. The dominating circulatory effect was a peripheral vasodilatation with increase in muscle and skin blood flow, flushing and fall of the arterial blood pressure. No effect was obtained on the blood pressures of the right heart. Heart rate and cardiac output increased.

The effect of substance P on the intestinal motility was studied both on isolated segments and intestine in situ. A marked increase in both segmental and peristaltic movements were observed, which was true both for normal subjects and in patients with intestinal paralysis.

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NEKI EFEKTI SP KOD ČOVJEKA

Zdravim licima davao se vrlo prečišćeni preparat SP putem intravenske infuzije. Periferna vazodilatacija s porastom protoka krvi kroz mišiće i kožu, pojavom crvenila i padom arterijskog krvnog pritiska, nastupila je kao dominantni cirkulatorni efekat. Nikakvo djelovanje nije zapaženo na krvni pritisak desne strane srca. Srčani ritam i srčani volumen bili su povećani.

Djelovanje SP na pokretljivost crijeva studirano je na izolovanim crijevnim segmentima, kao i na crijevu in situ. Zapaženo je znatno pojačanje segmentskih i peristaltičkih pokreta, i to kako kod normalnih lica tako i kod pacijenata s intestinalnom paralizom.

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DISCUSSION

HUKOVIĆ: Do the symptoms decrease during continued infusions of SP? What is it the subject feels like during the infusion of SP? The injection of crude SP in mice is followed in our experiments by a weakness of the skeletal muscles and, with great doses of SP, the complete paralysis of skeletal muscles could be seen *in vivo*. When you injected SP to yourself, could you feel any muscular weakness? Do you think that the changes in the blood flow could be due to the changes of muscle contractility?

PERNOW: Dr. Huković asked about the decrease in symptoms and effects during continued infusion. The effect was not due to a decrease in activity in the infusion solution, which was checked by assaying a proof of the infusion fluid after the end of the experiment. The decrease in effect seems to be rather due to a tachyphylaxis and is not specific for SP. If I am right, the same thing is seen for instance with H: intravenous infusion of H in the cat gives rise to an immediate fall in blood pressure, which is successively returning to the initial level, even during continued infusion. We never observed any muscular weakness during SP administration. I do not think that the effect of SP on the blood flow could be due to an effect on the muscular contractility since these studies were performed on resting subjects and since the blood flow increased not only in the muscles but also in the skin.

EULER: It would be of interest to study the content of SP in the intestine after periods of vagal stimulation. Preliminary experiments on rabbit have suggested that the vagus stimulation is followed by increased amounts of SP in the gut.

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