PHYSIOLOGY

Effect of Bombesin(6-14) on Arterial Pressure in Health and in Hypovolemic Shock

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Injection of active fragment of the neuropeptide bombesin(6-14) into cerebral ventricles of intact rabbits induces marked arterial hypertension accompanied by bradycardia and partial redistribution of blood to specialized heat-emitting organs (auricular conchae), which reduces body temperature. After a considerable blood loss, the peptide normalizes arterial pressure without affecting cardiac activity and body temperature. It is suggested that bombesins may be used for compensation of arterial hypotension during the early period of hypovolemic shock.

Key Words: *arterial pressure; blood loss; bombesin*

The use of massive blood transfusions and local vasoactive substances for the treatment of hypovolemic shock has a number of limitations [1,8,9], which prompts the search for agents acting on the central mechanisms of the vascular tone regulation. In the present study we evaluated the active moiety of the neuropeptide bombesin, Bn(6-14), as a candidate for such an agent.

Bombesin, a compound originally isolated from the skin of amphibia and then detected in the central nervous system and gastrointestinal tract of humans and higher animals, induces hypertension, hypothermia, and bradycardia when injected into cerebral ventricles or intrathecally [6].

MATERIALS AND METHODS

Male Chinchilla rabbits weighing 1.8-2.6 kg were used. Arterial pressure (AP) was measured in the carotid artery with a mercury manometer. Heart rate (HR) was estimated from an electrocardiogram recorded on an RFT Bioscript BST-1 polygraph (Czechoslovakia). Rectal and ear temperature was monitored with an electric thermometer (10 cm from the anal opening and 5 cm from the upper margin of the auricular concha) using a needle sensor. The temperature was recorded every 10 min over a period of 30 min before and 60 min after injection of Bn(6-14) (100 μg in 100 μl physiological saline) or 100 μl physiological saline (control group) into the lateral ventricle of the brain. The injection procedure was described previously [3].

In some rabbits, 28 ml of blood per kg body weight was removed through a catheter immediately before injection of Bn(6-14) or saline.

The ambient temperature was maintained at 20°C. The results were statistically analyzed by Student's test for paired and unpaired samples.

RESULTS

In intact rabbits, Bn(6-14) elevated AP by 21.5 mm Hg ($p<0.02$) and decreased HR by 70 beats/min ($p<0.01$) (Fig. 1); rectal temperature decreased in a uniform manner (being 0.93°C lower by the 45th min after injection; $p<0.02$) while the ear temperature

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increased. The mechanisms of these effects were discussed earlier [6]. Control group showed no significant changes in any of these parameters.

In experiments with blood loss, the baseline AP was 94.5±4.3 mm Hg in the test group and 98.5±1.6 mm Hg in the control group. After blood loss, AP decreased by 50-65 mm Hg ($p<0.01$). Central administration of saline did not alter AP: it remained at the level of 35.1±4.9 mm Hg. Bn(6-14) injected into the lateral ventricle increased AP by 44.4 mm Hg ($p<0.001$). The difference in AP between experimental and control animals was 50.3 mm Hg by the 20th min ($p<0.01$) and 31.2 mm Hg by the 50th min ($p<0.02$); thereafter, a tendency toward a decrease in AP was observed in the experimental group.

Blood loss reduced HR by 42.5 beats/min in experimental rabbits and by 50.5 beats/min in the controls. Neither Bn(6-14) nor saline had any significant effect on HR. When the intergroup difference in AP was the greatest (15 min after injection), that in HR was only 21 beats/min ($p>0.1$).

The baseline ear temperature was 28.2±2.0°C in experimental rabbits and 27.41±1.6°C in control rabbits. Neither blood loss nor subsequent injection of Bn(6-14) or saline significantly changed this parameter. The intergroup differences were also insignificant. By the 60th min postinjection, the mean ear temperature was 24.0°C in experimental and 23.9°C in control animals ($p>0.1$).

Rectal temperature decreased after blood loss by 0.76°C and 0.43°C in experimental and control groups, respectively ($p<0.05$), and continued to decline after intraventricular injection of Bn(6-14) or saline. Over 1.5 h, it fell by 2.98°C ($p<0.01$) in experimental and by 3.04°C in control rabbits ($p<0.01$). There was no intergroup difference in this parameter.

Our results indicate that intraventricular injection of Bn(6-14) normalizes AP reduced as a result of blood loss. It should be stressed that this effect is totally central, since bombesins cannot pass through the blood-brain barrier [5]. Normalization of AP is not associated with the action of this peptide on the central regulation of the heart. Blood loss itself led to a pronounced bradycardia. Under these conditions, bombesins cannot elicit a negative chronotropic effect.

In intact rabbits, intraventricularly administered Bn(6-14) markedly increased blood flow in the auricular conchae (specialized organs of heat emission), which is the main cause of the rapid decrease in body temperature [4]. A considerable decrease in the circulating blood volume leads to centralization of the circulation [2,7], therefore, an increase in blood flow through the auricular conchae is impossible. Since heat emission did not increase after central administration of Bn(6-14) against the background of blood loss, this peptide had no effect on the dynamics of rectal temperature.

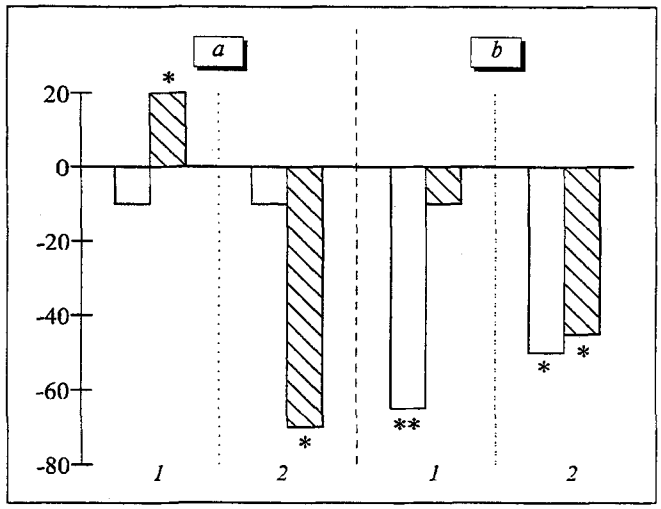

Fig. 1. Effects of intraventricularly injected bombesin(6-14) on arterial pressure (AP, *1*) and heart rate (HR, *2*) in rabbits with normal (*a*) and decreased (*b*) circulating blood volume. Control rabbits (white bars) received intraventricular injection of normal saline. The isoline marks the baseline AP and HR. Ordinate: increment in arterial pressure (mm Hg) or heart rate (beats/min). *$p<0.05$, **$p<0.01$ in comparison with the control group.

From these results it can be concluded that injection of the active bombesin moiety (C-terminal nonapeptide) into the cerebrospinal fluid after a massive blood loss normalizes AP mainly by virtue of the nonapeptide's ability to act on the central regulation of the vascular tone.

In clinical practice, this property of Bn(6-14) could afford more time for organizing and implementing effective blood substitution or avoid blood transfusion when it is contraindicated. Since lumbar puncture is an essential emergency measure in certain situations, injection of Bn(6-14) into the cerebrospinal fluid is feasible. The availability of bombesin-based drugs among antishock agents would facilitate subsequent therapeutic measures.

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