BLOCKING THE ANTIHYPERTENSIVE EFFECT OF CLONIDINE BY NALOXONE IN HYPERTENSIVE AND NORMOTENSIVE ANIMALS

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The centrally acting antihypertensive drug clonidine induces not only hypotension and bradycardia [5], but also analgesia [8]. The similarity between the effects of clonidine and opiates [8] suggests that interaction may take place between the opiate and α-adrenergic system of the brain. When this hypothesis was tested experimentally, different results were obtained: In dogs neither naloxone nor nalorphine abolished the hypotensive effect of clonidine [7] whereas in anesthetized rats a blocking action of nalorphine but not of naloxone was observed. According to Farsang et al. [4], naloxone abolishes clonidine hypotension only in rats with spontaneous hypertension, but not in normotensive animals. It is thus not yet clear whether there is an opiate component in the mechanism of the antihypertensive action of clonidine, or whether antagonism between clonidine and naloxone is confined to rats with spontaneous hypertension, and whether the blocking of the hypotensive effect of clonidine by naloxone is associated only with inhibition of vagal influences on the heart.

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized unrestrained cats, on anesthetized spontaneously hypertensive (SHR) rats, and on normotensive rats of the Wistar-Kyoto line (WKR).

The cats were anesthetized with pentobarbital and arterial and venous polyethylene catheters were implanted under sterile conditions [1]; the transducer of an electromagnetic flowmeter was placed on the ascending arch of the aorta of some animals in order to record the cardiac output (CO). The blood pressure (BP) was measured with an EMT-34 electromanometer (from Elema-Schonander, Sweden), CO by a type MG-64 flowmeter (from Nikon Kohden, Japan), and the momentary value of the heart rate (HR) was measured by a digital cardiotachometer, triggered by the pulse wave of BP. In the SHR and WKR rats BP was measured by means of a manometer in the carotid artery. The rats were anesthetized with urethane (600 mg/kg) and chloralose (50 mg/kg). All the parameters studied were recorded on a Mongograph-81 apparatus. Clonidine (from Boehringer Ingelheim, West Germany), in a dose of 10-30 μg/kg, naloxone (from Endo Laboratories, USA) in a dose of 0.15-1 mg/kg, and oxyphenonium bromide, which blocks muscarinic acetylcholine receptors (the Soviet preparation metacin), in a dose of 2 mg/kg, were injected intravenously.

All the SHR and WKR rats were divided into two groups. The animals of group 1 received naloxone at the peak of development of the hypotensive effect of clonidine, whereas the rats of group 2 received clonidine, oxyphenonium bromide, and naloxone consecutively.

The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

The total data on the effect of clonidine (10 mg/kg) on the BP and HR levels are made up of the results of experiments on the rats of groups 1 and 2 (18 SHR and 17 WKR). In the anesthetized SHR clonidine depressed BP from 117 ± 3.6 to 79 ± 5.6 mm Hg ($P < 0.01$) and HR from 364 ± 10.2 to 305 ± 13.7 beats/min ($P < 0.01$). In WKR clonidine produced a smaller fall in BP and HR. For instance, BP fell from 89.1 ± 2.8 to 68 ± 2.7 mm Hg and HR from 411 ± 12 to 370 ± 14.1 beats/min (for both parameters $P < 0.001$).

Injection of naloxone (1 mg /kg) into SHR rats ($n = 6$) against the background of the maximal lowering of BP and HR by clonidine, completely suppressed the hypotensive reaction and inhibited bradycardia by 60% (Fig. 1). In normotensive WKR rats ($n = 6$) naloxone reduced the hypotensive reaction by 76% but did not change the bradycardic response.

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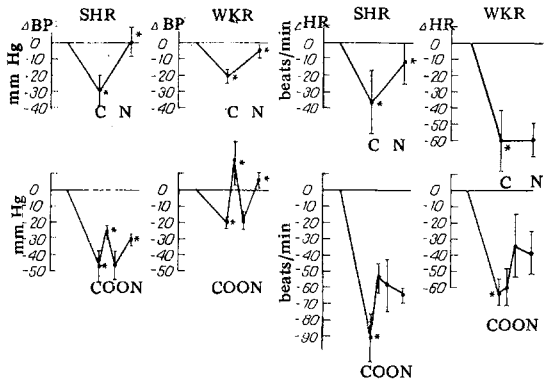

Fig. 1

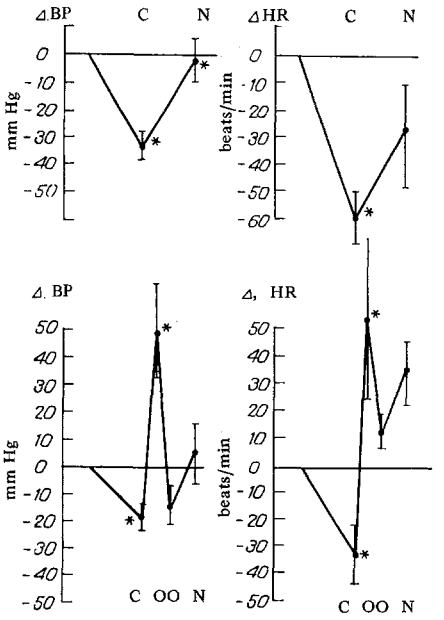

Fig. 2

Fig. 1. Changes in BP and HR of SHR and WKR rats. Top row shows effects of clonidine in a dose of 10 μg/kg (C) and naloxone in a dose of 1 mg/kg (N); bottom row shows effects of successive injection of clonidine in a dose of 10 μg/kg (C), oxyphenonium in a dose of 2 mg/kg (O), and naloxone in a dose of 1 mg/kg (N). The first measurement after injection of oxyphenonium corresponds to the maximum of the pressor response, the second was 5 min after injection of oxyphenonium. Asterisk indicates significant difference from values of previous measurement ($P < 0.05$).

Fig. 2. Changes in BP and HR of unanesthetized cats under the influence of clonidine in a dose of 30 μg/kg (C), oxyphenonium bromide in a dose of 2 mg/kg (O), and naloxone in a dose of 0.15 mg/kg (N). Legend and order of administration of drugs the same as Fig. 1.

To determine the role of the vagal component in the rise of BP under the influence of naloxone against the background of the maximal hypotensive reaction to clonidine, vagal influences of the heart were blocked in the SHR and WKR rats of group 2 by oxyphenonium bromide. Injection of this drug was followed by a sharp but brief (up to 5 min) rise of BP (Fig. 1). Under the influence of oxyphenonium HR increased for a period of over 5 min (Fig. 1). Blocking of opiate receptors by naloxone against the background of blocking peripheral muscarinic acetylcholine receptors led to a significant rise of BP in both SHR and WKR rats, but it did not affect HR (Fig. 1).

In unanesthetized cats naloxone (0.15 mg/kg) completely blocked the hypotensive effect and reduced the degree of bradycardia caused by clonidine by 55% (Fig. 2). Naloxone itself, even in doses of 2-8 mg/kg, did not alter the BP and HR levels and did not affect the central venous pressure or the blood flow in the superior mesenteric artery in anesthetized cats [2]. The increase in BP after administration of naloxone in these experiments thus indicated abolition of the hypotensive effect of clonidine.

Administration of oxyphenonium led to a greater transient increase in BP in the cats than in the rats. In animals under the influence of oxyphenonium, naloxone induced a significant increase in BP by 21 ± 7.3 mm Hg ($P < 0.05$) and an increase in HR by 21 ± 11.4 beats/min ($P = 0.1$) (Figs. 2 and 3).

The results of these experiments are evidence of antagonism between the effects of clonidine and naloxone in both SHR and WKR, although the effect of naloxone was weaker in the latter (Fig. 1). According to Karppanen, nalorphine, another blocker of opiate receptors, also blocked clonidine-induced hypotension and bradycardia in normotensive rats. The results of the present investigation thus do not agree with the observations of Farsang et al. [3, 4], who found that clonidine-naloxone antagonism is exhibited only by SHR rats.

Oxyphenonium bromide, in a dose of 2 mg/kg, completely blocked vagal influences on the heart, as was confirmed in these experiments by abolition of the baroreflex bradycardia evoked by an artificial rise of BP as a result of injection of phenylephrine (Fig. 3). In animals under the influence of oxyphenonium naloxone significantly increased BP in SHR and WKR rats and in unanesthetized cats, indirect evidence of activation of sympathetic neurons. The absence of tachycardia in SHR and WKR rats in response to injection of naloxone (in the group with oxyphenonium) suggests that the rise in BP

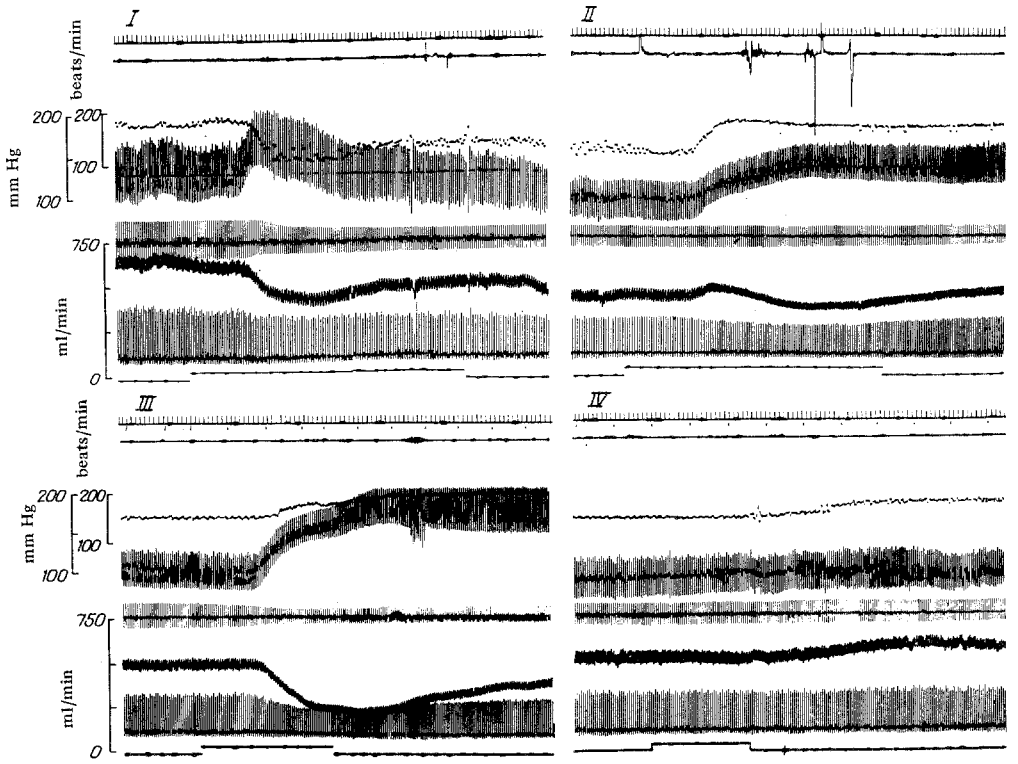

Fig. 3. Changes in principal hemodynamic parameters of unanesthetized cats under the influence of intravenous injection of clonidine in a dose of 30 μg/kg (I), oxyphenonium bromide in a dose of 2 mg/kg (II) and 40 μg/kg (III), and of naloxone in a dose of 0.15 mg/kg (IV). From top to bottom: time marker 1 sec, actogram, HR, BP, contractility of myocardium (dF/dt_{max}), cardiac output (integral), cardiac ejection (phasic), and marker of injection of drugs.

was due to an increased flow of vasoconstrictor impulses. In cats under the influence of oxyphenomium, naloxone raised both BP and HR, and this could indicate potentiation of sympathetic influences on the heart and vessels. The results of this investigation are in good agreement with those obtained by Laubie, who showed that activity in the splanchnic nerve is sharply increased by nalorphine, if injected after fentanyl [7] which, like clonidine, reduces background sympathetic activity. The neurochemical basis for the antagonism revealed between clonidine and naloxone may be the secretion of the endogenous opiate peptide β-endorphin, which has a powerful hypotensive action [6], in the brain under the influence of clonidine.

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