EFFECT OF CLONIDINE ON BLOOD PRESSURE, HEART RATE AND BODY TEMPERATURE IN CONSCIOUS RATS*

Hikaru OZAWA, Chin-Song CHEN, Hiroshi WATANABE and Toshio UEMATSU
Department of Pharmacology, Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
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Abstract—Effects of clonidine on blood pressure, heart rate and rectal temperature in conscious rats were examined. Clonidine (0.1-1 mg/kg s.c.) caused a prevailing pressor response and dose-dependently a fall in heart rate and body temperature. The pressor response to clonidine (0.3 mg/kg s.c.) was completely reduced by phentolamine (10 mg/kg s.c.), chlorpromazine (10 mg/kg s.c.) but not by hexamethonium (30 mg/kg i.p.), guanethidine (30 mg/kg s.c.) or reserpine (5 mg/kg s.c. 18 hr + 1 mg/kg i.p. 4 hr prior to clonidine). Conversely, a remarkable potentiation of the pressor response to clonidine was observed after treatment with reserpine. The bradycardia with clonidine (0.3 mg/kg s.c.) was significantly reduced by phentolamine, chlorpromazine or atropine (5 mg/kg s.c.) but was potentiated by reserpine. The hypothermia with clonidine (0.3 mg/kg s.c.) was not influenced by phentolamine or atropine but was significantly potentiated by chlorpromazine. From the above results it is suggested that the prevailing pressor response to clonidine in conscious rats is due to a stimulation of peripheral a-adrenoceptors, the bradycardia with clonidine is exerted through the sympathetic pathway and the baroceptor-vagal reflex, and that the hypothermia with clonidine is mainly due to the central mechanism.

In anesthetized animals, clonidine shows a biphasic blood pressure response, which consists of an initial prompt rise and a delayed long lasting fall in blood pressure with a durable bradycardia (1-3). It is suggested that the rise and the fall in blood pressure with a bradycardia induced by clonidine is due to a stimulation of peripheral and central a-adrenoceptors, respectively (4-9). However, in conscious animals, clonidine shows a blood pressure response which the rise in blood pressure prevails to the fall. This rise in blood pressure is thought to be due to a central mechanism (10). Besides the cardiovascular effects, clonidine causes a remarkable fall in basal rectal temperature in rats (11). Whether the hypothermia with clonidine is mediated through either the peripheral or the central mechanism, or both mechanisms remains to be clarified.

The present study was undertaken to clarify the precise mechanism of the prevailing rise in blood pressure with a bradycardia induced by clonidine in conscious rats, and in addition, the correlation between the cardiovascular and the hypothermic mechanisms of clonidine.

MATERIALS AND METHODS

Male Wistar rats weighing 250-300 g were used. Under anesthesia with a-chloralose

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(80 mg/kg i.v.)-urethane (500 mg/kg i.v.) systemic blood pressure was recorded from the right common carotid artery via a pressure transducer (Nihon Kohden, MPU-0.5) on a polygraph (San-ei Instrument, 8S), and simultaneously heart rate was recorded using a pulse rate tachometer (San-ei Instrument, 2130) triggered by the pulse of the blood pressure. According to the method of Weeks and Jones (12), systemic blood pressure and heart rate in conscious rats were recorded from the abdominal aorta using the above described instruments. The recording of blood pressure was done 3 days after the operation. Using different male Wistar rats (250-300 g) from those in the case of blood pressure, the rectal temperature was recorded via a thermister (Shibaura Electronics, MGA-3) inserted into the rectum at a distance 5 cm from the anus. The experiment was carried out in a room where the temperature was maintained at 24 ± 1°C.

Drugs used were clonidine hydrochloride (Boehringer Sohn), phentolamine mesylate (Regitine, CIBA-Geigy), chlorpromazine hydrochloride (Wintermin, Shionogi), desipramine hydrochloride (Pertofran, Fujisawa), hexamethonium bromide (Methobromine, Yamanouchi), atropine sulfate (Wako Chemicals), guanethidine sulfate (Ismeline, Takeda) and reserpine (Apoplone, Dai-ichi).

All drugs were dissolved in physiological saline, and the solutions (1 ml/kg) were injected intravenously through the inserted cannula into the left jugular vein, subcutaneously or peritoneally. All doses are expressed as mg/kg of salts except for reserpine.

Statistical analysis was done using the Student’s t-test.

RESULTS

Time course of changes in blood pressure, heart rate and body temperature of conscious rats after subcutaneous injection of clonidine

Clonidine (0.1-1 mg s.c.) causes a remarkable and relatively durable rise in blood pressure in conscious rats. The rise in blood pressure induced by clonidine (0.3 mg s.c.)

![Fig. 1. Time course of changes in mean blood pressure, heart rate and body temperature of conscious rats after s.c. injection of clonidine. Clonidine was injected at zero time. N's and vertical bars indicate the number of animals and standard errors, respectively.](image-url)
was followed by a delayed long lasting fall, but the latter response was not always observed with all doses of clonidine during the experiment. On the other hand, clonidine (0.1–1 mg s.c.) caused dose-dependently a long lasting fall in heart rate and body temperature of conscious rats. These data are summarized in Fig. 1.

Effects of phentolamine and chlorpromazine on changes in blood pressure, heart rate and body temperature induced by clonidine in conscious rats

The rise in blood pressure and the bradycardia induced by clonidine (0.3 mg s.c.) were significantly reduced 30 min after treatment with phentolamine (10 mg s.c.) or chlorpromazine (10 mg s.c.) (p<0.01). A reversal of blood pressure was sometimes observed by clonidine after treatment with these α-adrenoceptor blocking agents. The hypothermia with clonidine (0.3 mg s.c.) was not influenced by phentolamine (10 mg s.c.) but was remarkably potentiated after treatment with chlorpromazine (10 mg s.c.). Phentolamine (10 mg s.c.) or chlorpromazine (10 mg s.c.) itself caused a considerable fall in blood pressure, a remarkable tachycardia and a significant hypothermia (p<0.01). These data are shown in Figs. 2 and 3.

Fig. 2. Effect of phentolamine on changes in mean blood pressure, heart rate and body temperature of conscious rats after s.c. injection of clonidine. Clonidine was injected at zero time. Phentolamine was injected s.c. 30 min prior to clonidine. Other points as in Fig. 1.

Fig. 3. Effect of chlorpromazine on changes in mean blood pressure, heart rate and body temperature of conscious rats after s.c. injection of clonidine. Time of clonidine and chlorpromazine injection and other points as in Fig. 2.
Effect of desipramine on changes in blood pressure, heart rate and body temperature induced by clonidine in conscious rats

The rise in blood pressure and the bradycardia induced by clonidine (0.3 mg s.c.) in conscious rats were significantly potentiated 30 min after treatment with desipramine (10 mg s.c.) (p<0.1), and the delayed fall in blood pressure with clonidine (0.3 mg s.c.) was not observed during the experiment. Desipramine (10 mg s.c.) itself did not significantly influence the blood pressure (p>0.1) but did cause a slight fall in heart rate and body temperature. These data are shown in Fig. 4.

Effect of atropine on changes in blood pressure, heart rate and body temperature induced by clonidine in conscious rats

After treatment with atropine (5 mg s.c.) the initial rise and the delayed fall in blood pressure induced by clonidine (0.3 mg s.c.) were slightly potentiated, while the bradycardia
with clonidine (0.3 mg s.c.) was significantly inhibited (p<0.01). The hypothermia with clonidine (0.3 mg s.c.) was not significantly influenced by atropine (5 mg s.c.) (p>0.1). Atropine (5 mg s.c.) itself did not show any significant effect on blood pressure and body temperature (p>0.1) but caused a significant increase in heart rate (p<0.01). These data are shown in Fig. 5.

Effects of hexamethonium, guanethidine and reserpine on the rise in blood pressure and heart rate induced by clonidine in conscious rats

The rise in blood pressure induced by clonidine (0.3 mg s.c.) in conscious rats was not reduced, but was slightly potentiated after treatment with hexamethonium (30 mg i.p.) or guanethidine (30 mg s.c.). On the other hand, the rise in blood pressure and the bradycardia with clonidine (0.3 mg s.c.) were markedly potentiated by reserpine (5 mg s.c. 18 hr plus 1 mg

![Fig. 6. Effect of hexamethonium on the pressor response to s.c. injection of clonidine in conscious rats. Time of drug injection and other points as in Fig. 2.](image)

![Fig. 7. Effect of guanethidine on the pressor response to s.c. injection of clonidine in conscious rats. Time of drug injection and other points as in Fig. 2.](image)

![Fig. 8. Effect of reserpine on the pressor response to s.c. injection of clonidine in conscious rats. Clonidine was injected at zero time. Reserpine was injected s.c. in a dose of 5 mg/kg 18 hr and i.p. in a dose of 1 mg/kg 4 hr prior to clonidine. Other points as in Fig. 2.](image)
i.p. 4 hr before). The delayed fall in blood pressure with clonidine (0.3 mg s.c.) was not observed after treatment with these agents during the experiment. These data are shown in Figs. 6, 7 and 8.

Comparison between the blood pressure responses and heart rate after intravenous injection of clonidine in anesthetized and conscious rats

Clonidine (0.1 mg i.v.) caused a durable fall in blood pressure and heart rate of anesthetized rats, and a considerable and relatively durable rise in blood pressure with a remarkable bradycardia in conscious rats. Fig. 9 shows the time course of changes in blood pressure and heart rate after intravenous injection of clonidine in anesthetized and conscious rats.

DISCUSSION

It is characteristic that clonidine shows a relatively longer-lasting rise in blood pressure of conscious rats than that in anesthetized ones. Trolin (10) recently suggested that the pressor response to a higher dose of clonidine (100 μg/kg i.v.) in conscious rats is due to a central mechanism. However, the present experiments in conscious rats indicate that the prevailing pressor response to clonidine is due to a direct peripheral α-sympathomimetic action of the drug, since the response to clonidine is completely inhibited after treatment with an α-adrenoceptor blocking agent, but not by a ganglion blocking agent or adrenergic neuron blocking agent. Brezenoff (13) has recently reported that the cardiovascular response to norepinephrine in conscious rats is influenced by various anesthetic agents. It is possible that the cardiovascular response to clonidine is also depressed in states of anesthesia. In addition, the pressor response to clonidine in conscious states is more or less potentiated by pretreatment with hexamethonium, guanethidine, reserpine or atropine. We consider that pretreatment with these agents during a state of consciousness causes a hypersensitivity of the cardiovascular system to clonidine, but the precise mechanism remains to be clarified. In particular, pretreatment with reserpine during a state of anesthesia is considered to cause a supersensitivity of the cardiovascular system (14, 15). In general, short-term pretreatment with reserpine, even in a large dose, does not result in a supersensitivity of the innervated organs. The time factor for supersensitivity with reserpine does, however, vary with the organ. Supersensitivity of the cardiovascular system develops with 2 or 3 days of long-term pretreatment (14, 15), while in other innervated organs this supersensitivity develops only after 7 days (15, 16). The difference in the magnitude of the time course between organs is attributed to the fact that in intact animals, the blood vessels and cardiac tissues receive a much larger number of impulses per unit time than the other innervated organs or
tissues (17). If such is indeed the case, a much shorter-term pretreatment with reserpine would produce a supersensitivity of the cardiovascular system in conscious states. It has been reported that the depressor response to clonidine is markedly reduced by desipramine (18, 19), and conversely, not modified by pretreatment with desipramine (8). From the present experiments, it is deduced that the slight potentiation of the pressor response to clonidine after treatment with desipramine is not due to the reduction of the depressor response, but rather to the non-specific sensitization of the cardiovascular system to clonidine such as is seen after treatment with hexamethonium, guanethidine, atropine, etc.. A slight potentiation of the bradycardia with clonidine after treatment with desipramine is probably the result of further stimulation of the central mediated vagal reflex due to the potentiation of the pressor response to clonidine.

Thus, the bradycardia with clonidine is apparently exerted in part through a baroceptor-vagal reflex which is triggered by the pressor response to the drug, since the bradycardia with clonidine is significantly reduced by atropine or an α-adrenoceptor blocking agent. This reduction of the bradycardia with clonidine by an α-adrenoceptor blocking agent is assumed to be due to a decrease in the baroceptor-vagal reflex which is triggered by the blood pressure. Reduction of the bradycardia to clonidine is, however, partly due to an antagonism of the presynaptic inhibition of the drug on the cardiac sympathetic nerve terminals by an α-adrenoceptor blocking agent (20, 21). Reserpine shows a significant potentiation of the bradycardia to clonidine in conscious rats and this potentiation is considered to be caused by summation of the activities of the baroceptor-vagal reflex with a combination of clonidine and reserpine, since it is well known that reserpine itself causes a vagal stimulation as a result of the increase in the central parasympathetic activity (22–25).

It has already been reported that a systemic application of certain α-sympathomimetic agents, naphazoline, oxymetazoline, clonidine, etc., to rats causes a fall in body temperature only (26). It seems that peripheral and central α-adrenoceptors are involved in the hypothermia induced by these agents. The results of the present experiments, however, strongly suggest that the hypothermia with clonidine originates mainly in the central mechanism, since the hypothermia with clonidine is not reduced after treatment with phentolamine. On the other hand, it has been reported that a central application of norepinephrine causes either a rise or a fall in body temperature of rats depending on the injection sites of the drug in the brain (27–30). Therefore, we consider that clonidine causes predominantly a stimulation of the α-adrenoceptors which are involved in the norepinephrine-induced hypothermia. Why chlorpromazine potentiates the hypothermia with clonidine is not clear, but it is certain that the α-adrenoceptors sensitive to clonidine are resistant to chlorpromazine. However, there may be a synergism between the hypothermia of clonidine and chlorpromazine, since the former is thought to originate in the central mechanism and the latter in the peripheral mechanism (26, 31).

From the above findings it is suggested that clonidine causes predominantly a pressor response in conscious rats due to a direct stimulation of peripheral α-adrenoceptors, that the bradycardia with clonidine is exerted through the sympathetic pathway and in part
through the baroceptor-vagal reflex, and that the hypothermia with clonidine is mainly due to the central mechanism.

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