The Effect of Isopropylamino Radical on the Cardiovascular System

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IN 1948, AHLQUIST¹ postulated two types (α and β receptors) of adrenergic receptors. But his hypothesis was not widely accepted. Since β -blocking agents have been developed, his theory has come to be supported. Moreover, a relation between α and β receptors and the structure of sympathomimetic agents has interested many investigators. ARIËNS^{2,3} and BELLEAU advocated a hypothesis of the action of those agents to both receptors. ARIËNS reported that the amino radical of catecholamine related to the action of α -receptor, and dihydroxyphenyl radical was required to the action of β -receptor. However, when the action of sympathomimetic agents was examined systematically, ARIËNS' hypothesis failed to explain completely the relation of the action of receptors and the structure of those agents.

6-amino-2-methyl-2 heptanol (Heptamin) had a sympathomimetic action, even though the drug had no phenol or phenyl radical. Isopropylamino-6-methyl heptane (Metron) also had no phenyl radical but still had isopropylamino radical. Pronethalol has a naphthalene group and isopropylamino radical.

The present authors tried to examine both drugs in dogs to confirm the effect of isopropylamino radical on the cardiovascular system (blood pressure and heart rate) and to discuss a role of this radical to adrenergic receptors.

MATERIAL AND METHOD

Mongrel dogs of about 10 kg were anesthetized by pentobarbitul and a catheter was inserted into the femoral artery to measure systolic and diastolic blood pressure at the aorta. STETHAM's manometer was used to measure blood pressure and heart rate

was calculated on lead II. A recorder of American Commercial Co. was used.

The following drugs were injected intravenously as quickly as possible. Blood pressure (systolic and diastolic pressure) and ECG were recorded during the first one minute, at 1'30, at 2' and 3' after the start of injection. Each datum from recordings was plotted on the graph.

The drugs injected for groups of 2 or 3 dogs were as follows :

- 1) Isoproterenol (Ispurel)
- 2) 3-5-dihydroxyphenyl-2-isopropylamino ethanol (Alotec)
- 3) 4-hydroxyphenyl-2-butylaminoethanol (Vasculat)
- 4) Isoxsuprine (Duvadilan)
- 5) 6-amino-2-methyl-2-heptanol (Heptamin)
- 6) Pronethalol (Nethalide)
- 7) 2-isopropylamino-6-methyl heptane (Metron)

RESULTS

1) Isoproterenol (Fig. 1)

After 0.02 mg/kg of isoproterenol was injected quickly into the femoral vein, systolic pressure elevated temporarily followed by a decrease. Diastolic pressure decreased. Heart rate also increased markedly. Thereafter systolic pressure returned to the control level 2 minutes after the start of injection.

2) 3-5-dihydroxyphenyl-2-isopropylamino ethanol (Alotec) (Fig. 1)

Injection of 0.05 mg/kg of Alotec caused a temporary elevation of systolic pressure and a depression of systolic and diastolic pressure as in injection of isoproterenol. Heart rate also increased markedly. Blood pressure and heart rate did not return to the control level 3 minutes after injection.

3) 3-hydroxyphenyl-2-butylaminoethanol (Vasculat) (Fig. 2)

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Injection of 0.5 ms/kg of this drug produced a depression of systolic and diastolic pressures without a transient elevation of systolic pressure. The heart rate increased moderately.

4) Isoxsuprine (Fig. 2)

Following injection of 0.5 mf/kg of isoxsuprine, systolic pressure remained at a control level after a slight elevation. On the other hand, a depression of diastolic pressure and an increase of heart rate were observed

Fig. 1. Changes of heart rate (Hr ---), maximal blood pressure (Max —) and minimal blood pressure (Min —) after injection of isoproterenol (0.02 mg/kg) and Alotec (0.05 mg/kg) C=control, 1=1 minute after injection, 100=100 mmHg in blood pressure, or 100/min in heart rate).

Fig. 2. Changes of heart rate and blood pressure after injection of Vasculat (0.5 mg/kg) and Duvadilane (0.5 mg/kg).

Fig. 3. Changes of heart rate and blood pressure after injection of pronethalol 5.0 mg/kg and isoproterenol (IP 0.02 mg/kg).

Fig. 4. Changes of heart rate and blood pressure of Metron (2.0 mg/kg or 5.0 mg/kg).

for 3 minutes after injection.

5) 6-amino-2-methyl-2-heptanol (Heptamin)

This drug was used to elevate blood pressure. After injection of 20–50 mg/kg of this drug, the heart rate increased and blood pressure markedly elevated and the elevated blood pressure was blocked following injection of 0.5 mg/kg of regitine.

6) Pronethalol (Fig. 3)

When 5.0 mg/kg of pronethalol, a β -blocking agent, was injected, a slight increase of heart rate and a slight depression of blood pressure were observed, and this drug also reduced a fall of blood pressure and an increase of the heart rate induced by injection of 0.02 mg/kg of isoproterenol. However, injection of

10.0 mg/kg of this drug caused a decrease of heart rate and a fall of blood pressure.

7) 2-isopropylamino-6-methyl heptane (Metron) (Fig. 4, 5 and 6)

Injection of 2.0 mg/kg of Metron caused a slight depression of systolic and diastolic pressures and a slight increase of heart rate. Those changes were disappeared soon. When 5.0

mg/kg of this drug was injected, a moderate decrease of systolic and diastolic pressure and a decrease of heart rate were observed (Fig. 4). However, following premedication of 0.02 mg/kg of atropine, injection of 5.0 mg/kg of this drug caused a slight depression of blood pressure with a slight increase of heart rate which was observed after injection of 2.0 mg/kg of this drug alone (Fig. 5).

After injection of 0.5 mg/kg of propranolol, injection of 2.0 mg/kg or 5.0 mg/kg of Metron produced a more significant fall of blood pressure than after injection of Metron alone. The heart rate still remained at a level subsequent to injection of propranolol (Fig. 6).

DISCUSSION

It has been well known that noradrenaline and adrenaline elevated and isoproterenol decreased blood pressure, but adrenaline after pretreatment of ergotamine alkaloid decreased it. About 20 years ago AHLQUIST presented that α and β preptors existed in an adrenergic receptor. Although α -blocking agents were already discovered, β -blocking agents which are necessary to prove his theory have been only recently produced. The first agent of a β -blocking agent was DCI (Dichloroisoproterenol), in which two OH radicals in isoproterenol

Fig. 5. Changes of heart rate and blood pressure after injection of Metron (5.0 mg/kg) following the premedication of atropin sulfate.

Fig. 6. Changes of heart rate and blood pressure (5.0 mg/kg) following the premedication of propranolol-inalderal (0.5 mg/kg).

were replaced with two Cl radicals. Propranolol has been developed to be used clinically and discovery of a β -blocking agent is likely to prove the α - β receptor theory by AHLQUIST. On the other hand, when the side chain of catecholamine was substituted for another radical, injection of that agent caused an elevation or depression of blood pressure depending upon different structures of amino radical. KONZETT⁶ reported that when the amino radical of catecholamine was substituted for propylamino, butylamino or isopropylamino radical, a blood pressure decreased. Therefore, ARIËNS presented a hypothesis concerning a relation of the structures of those agents and α , β receptors. According to his hypothesis, an α action was related with the amino radical and an increase in the number of carbon caused a decrease of an α action. On the contrary, two OH radicals of catechol radical were required for a β action and a β action appeared when an α action decreased due to an increase in the number of carbon in amino radical. His opinion was supported by a β blocking action of DCI, in which two OH radicals were replaced with two Cl radicals. He also described that an agent with one OH radical (hydroxyphenyl radical) had still an affinity for β -receptor, and an agent without OH-radical had no β sympathomimetic action.

In fact, the action on blood pressure by Adrianol (3-hydroxyphenyl-2-methyl amino-ethanol) was weaker than that by adrenaline⁶. However, 3-hydroxyphenyl, 4-hydroxyphenyl and even phenyl-isopropyl amino-ethanol decreased blood pressure⁶.

In the present study, isoxsuprine with a hydroxyphenyl radical produced an apparent fall of blood pressure and an increase of heart rate.

If ARIËNS' hypothesis would be true, agents which had no OH radical might have no β action. However, pronethalol which had a naphthalin group with isopropylamino radical, a β -blocking agent, was reported to have a β action. Therefore, in order to confirm a relation of a β action and OH radical⁸ in benzene, the present authors tried to examine the action of pronethalol and Metron⁷ which had isopropylamino radical. When 2.0 mg/kg of Metron

was injected intravenously, a slight fall of blood pressure and a slight increase of heart rate were observed, but 5.0 mg/kg of that drug caused a bradycardia with a fall of blood pressure. However, after pretreatment of atropine, injection of 5.0 mg/kg caused a result similar to injection of 2.0 mg/kg alone. Consequently, bradycardia caused by injection of 5.0 mg/kg alone might be due to a vagal stimulation of Metron, and it was supposed that a change after injection of 2.0 mg/kg of Metron was due to mild stimulus on β action. After injection of isoproterenol or Alotec, a transient elevation of systolic pressure was observed, which was apparently caused by the inotropic effect of those drugs. That phenomenon was not found after injection of Metron or pronethalol, because a β action of those drugs might be milder than that of isoproterenol and Alotec.

Of course, it cannot be said that a fall of blood pressure with an increase of heart rate is equal to a β action. However, it was reported that pronethalol had a β action, and in the present study, an action of Metron has been found very similar to that of pronethalol. But after pretreatment of propranolol, injection of Metron caused a more marked fall of blood pressure than after injection of Metron alone. It is assumed that this phenomenon might be produced by a vagal stimulation or another action of Metron after the disappearance of a β action due to injection of propranolol.

If Metron had only a β action, a fall of blood pressure should disappear following pretreatment of propranolol. If a fall of blood pressure due to Metron had no relation to a β action, a similar degree of a fall might appear following pretreatment of propranolol. Therefore this phenomenon may be caused by another action of Metron.

According to the present results, a remarkable β action in cardiovascular system (a fall of blood pressure with a transient elevation of systolic pressure and a marked increase of heart rate) is caused by an agent with isopropylamino radical and dihydroxyphenyl radical. But injection of an agent with isopropylamino radical without dihydro or hydroxyphenyl radical causes a mild β action (a slight fall of blood pressure and a slight increase of heart rate).

Therefore, it seems reasonable to consider that the intensity of a β action depends on the structure of dihydroxyphenyl radical, but a β action itself originates in the structure of amino radical.

SUMMARY

1. In order to reexamine ARIËNS' hypothesis concerning a relation of an α and β action and the structure of catecholamine, an attempt was made to examine effects of pronethalol and 2-isopropylamino-6 methyl heptane (Metron) on blood pressure and heart rate in dogs.

2. Injection of 5.0 mg/kg of pronethalol caused a slight increase of heart rate and a slight fall of blood pressure, but injection of 10.0 mg/kg resulted in bradycardia and a marked fall of blood pressure.

3. When 2.0 mg/kg of Metron was injected, a transient increase of heart rate and a fall of blood pressure were observed, but after injection of 5.0 mg/kg, a bradycardia and a fall of a blood pressure were caused. When 5.0 mg/kg of Metron was injected after pretreatment of atropine, changes similar to those after injection of 2.0 mg/kg were observed.

4. A slight increase of heart rate and a fall of pressure after injection of pronethalol or Metron seem to indicate a mild β action. But

following an increase of dosage of those drugs, a vagal omimetic action appeared, and a β action was not observed. However, pretreatment with atropine reproduced a β action.

5. Pronethalol and Metron had no catechol or phenyl radical, but still possessed a mild β action. Therefore, a β action seemed to relate to isopropylamino radical, and dihydroxyphenyl or hydroxyphenyl radical might be related with an increase of the intensity of a β action.

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