Effect of Isopropylamino Radical and Isoquinoline Derivatives on Cardiovascular System

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The present authors reported that isopropylamino radical had the effect of adrenergic \( \beta \) actions on cardiovascular system. Those \( \beta \) actions were found in some agents of \( \beta \) blockers and in an agent without phenyl radical. Therefore it was stressed that \( \beta \) actions had not related to dihydroxyphenyl or hydroxyphenyl radical, but to numbers of \( CH_3 \) in amino radical.

Recently, KIYOMOTO and his coworkers proved that one of tetrahydroisoquinoline derivatives had a stronger bronchodilating action than isoproterenol, but a milder effect on cardiovascular system. As it was very interesting that isoquinoline derivatives has a \( \beta \) action, to the present paper, authors compared the effect of agents with isopropylamino radical and tetrahydroisoquinoline derivatives on cardiovascular system and discussed a relation between \( \beta \) actions and chemical structures.

MATERIALS

Mongrel dogs were anesthetized with pentobarbital.

Lead II in ECG and blood pressure in femoral artery were recorded with Sanborn's multirecorder and Stetham's manometer. Heart rate (HR), systolic blood pressure (maximal pressure-MAX) and diastolic blood pressure (minimal pressure-MIN) were calculated at each point before injection, each 10th second of the first one minute after injection, at the one and half minute, at the second minute and the third minute after injection. Each datum was plotted as shown in Fig.1.

The agents used in the present experiment were as follows:
1) Isoproterenol (Proterenol L)
2) AQL-208 1-(3', 4', 5'-trimethoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline
3) No. 266 1-benzyl-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline
4) No. 806 1-(3', 4'-ethylenedioxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline
5) E241 2-chlorophenyl-isopropylamino-ethanol
6) Alprenolol (H 56/28) 1-(2-allylphenoxy)-3-isopropyl-aminopropanol (2)
7) Trasicor (CIBA 39.089-Ba) 1-(0-allyloxyphenoxy)-3-isopropylaminopropanol (2)

RESULTS

1) Isoproterenol (Fig.1)

Isoproterenol was used to compare the effect of AQL-208 on cardiovascular system. 0.01 mg, 0.02 mg, 0.001 mg, 0.5 \( \mu \)g, 0.25 \( \mu \)g per kg of IP were injected intravenously. In all cases, heart rate increased and diastolic pressure decreased. Systolic pressure elevated initially and thereafter fell in cases injected with a large dosage of IP. However, in cases with injection of 0.25 \( \mu \)g/kg, systolic pressure elevated for a few minutes with a fall of diastolic pressure.

2) AQL-208 (Fig.1-4)

AQL-208 was injected with same dosage of IP. After injection of 0.02 mg/kg of AQL-208, heart rate increased and systolic and diastolic pressure decreased. Those actions were blocked by propranolol.

In cases with small dosage (0.25 \( \mu \)g/kg) of injection, systolic pressure elevated and diastolic pressure fell. The chronotropic effect of AQL was less than but the duration of these actions was longer than those of Isoproterenol (Fig.3).

The same result of the chronotropic effect was obtained after injection of 0.125 \( \mu \)g/kg of Isoproterenol and AQL.
3) No.266 (Fig.5)
   When 0.02 mg/kg of No.266 was injected, heart rate increased moderately and diastolic pressure fell. Systolic pressure initially decreased, but elevated gradually. Those actions were blocked by a β blocker.
4) No.806 (Fig.6)
   The effect of No.806 on cardiovascular system was mild, even though 0.1 mg/kg of No.806 was injected.
5) E 241 (Fig.7)

This agent also had minimal actions to heart rate and blood pressure, and had no action of a β blocker.
6) Alprenolol (Fig.8, 9)
   Alprenolol had a β blocking action. However, when 0.09-0.1 mg/kg of Alprenolol was injected, heart rate increased slightly and blood pressure also decreased. After injection of 0.125 mg/kg, heart rate decreased.
7) Trasicor (Fig.10)
   This drug also was a β blocking agent. The

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Fig. 3. Heart rate and blood pressure after injection of a small dosage (0.25 μg/kg) of AQL and IP.

Fig. 4. Increasing ratio of heart rate and blood pressure after injection of 0.25 μg/kg of IP and AQL.

Fig. 5. Heart rate and blood pressure after injection of No. 266. (0.02 mg/kg)

Injection of 0.1 mg/kg of Trasicor caused a decrease of heart rate.

DISCUSSION

Since AHLQUIST's hypothesis of adrenergic α and β receptors, the relation between the structure of catecholamine and α or β actions were investigated by many pharmacologists. ARJENS postulated that β action related to dihydroxyphenyl radical.

But the present authors denied that hypothesis in the preceding paper, because metron and pronethalol which had no dihydroxyphenyl or hydroxyphenyl radical still showed a β action or β like action. Therefore, it was assumed that the amino radical had a β or α action depending
on the numbers of carbon.

In the present paper, it was demonstrated that Alprenolol had a mild $\beta$ action in a small dosage. ABLAD et al. also reported a $\beta$ action of Alprenolol which was blocked by pronethalol. Even though the present authors failed to show a $\beta$ action of Trasicor, a $\beta$ action of Trasicor was reported.

E241 (2-Chlorophenyl-isopropylamino-ethanol) also had mild action of increase of heart rate and decrease of blood pressure.

Then it was confirmed that isopropyl amino radical had played an important role to a adrenergic $\beta$ action and dihydroxyphenyl radical acted to increase potency of $\beta$ action.

KIYOMOTO and his co-workers investigated the effects of tetrahydroisoquinoline derivatives on bronchial muscle. They found that AQL-208 had the most potency of bronchodilator and those derivatives had also a $\beta$ actions. They described that the bronchodilating action of AQL was very stronger but the effect on cardiovascular system was somewhat weaker than those of isoproterenol. Therefore the action of cardiovascular system of...
AQL was less than that of isoproterenol, when a dosage of AQL equivalent to that of IP to pre- 
duse a some degree of bronchodilation was used.

Tetrahydro-isoquinoline derivatives had 6-7 dihydroxy group and showed a structure similar to catecholamine. AQL-208 had a strong bron- 
chodilating action, but the 4-piperidemethyl analogue or other analogue had not such an ac-
tion. Consequently, a bronchodilating action of tetrahydro-isoquinoline depended on the struc-
ture of R which was combined with tetrahydro-
isoquinoline eventhough the derivatives without 6-7 dihydroxy had little effect of a β action.

In the present experiments, it was proved that AQL-208 had inotropic, chronotropic and 
vasodilating actions similar to isoproterenol, but actions of No.266 and No.806 were weaker than 
that of AQL-208. The effect of tetrahydro-
isoquinoline derivatives on cardiovasvular system 
also depended on the structure of R (Fig.11).

Therefore, β actions of tetrahydro-isoquinoline 
derivatives may by related to the structure of R, 
eventhough 6-7 dihydroxy radical has some im-
portant role of a action in those derivatives.
Fig. 10. Heart rate and blood pressure after injection of Trasicor and that 
β blocking action.

![Chemical Structures]

It is concluded that in agents with isopropylamino radical and tetrahydro-isoquinoline derivatives, adrenergic β actions are not based on dihydroxyphenyl radical, but on the compound combined with N. Of course, compounds in agents with isopropylamino radical and in tetrahydroxy-
isoquinoline derivatives are somewhat different. In the former, isopropylamino radical is combined with N, but in the latter, the arylmethyl analogue is combined with tetrahydro-isoquinoline, and the structures of tetrahydro-isoquinoline derivatives are rather similar to Caytine or Nylidrine.

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SUMMARY

The effects of isopropylamino radical and tetrahydro-isoquinoline derivatives on the cardiovascular system were investigated.

It was proved that agents with isopropylamino radical, and no dihydro or hydroxyphenyl radical caused a mild action of increasing of heart rate and fall of blood pressure.

On the other hand, an agent of tetrahydro-isoquinoline derivatives with dihydro radical had actions similar to those of isoproterenol. But those actions had a close relation to the structure combined with tetrahydro-isoquinoline.

Therefore, the actions of increasing heart and falling blood pressure was not fundamentally related to dihydroxyphenyl or hydroxyphenyl radical.

REFERENCES


