Regular Articles

Effects of Xylopinine on the Spontaneous Movements of the Isolated Guinea-pig's Atria

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The effects of xylopinine on the adrenergic mechanism of the isolated guinea-pig's atria were studied. Xylopinine in concentrations above 10^{-8} depressed the rate of the atrial beat without affecting the concentration. During the early phase of the atrial depression by xylopinine the chronotropic effects of adrenaline and isopropylnoradrenaline were depressed, while the same effects were potentiated during the late phase of the depression.

Schmutz[2] was the first to isolate xylopinine (*l*-norcoralydine) (I), the tertiary amine base of the tetrahydroprotoberberine type, as well as discretine and discretinine from *Xylopia discreta* L.f. belonging to the Anonaceous plants. The structurally similar quaternary ammonium base, phellodendrine (II), was isolated from *Phllodendron amurense* RUPR. by Tomita and Nakano[3] and was determined its structure by Tomita and Kunitomo.[4] Among the derivatives of tetrahydroprotoberberine, cyclanolne (III) and steponine (IV) of the palmatine type,[5,6] phellodendrine[7] and xylopinine[8-10] have been pharmacologically investigated. The former three ammonium bases were described to exhibit the ganglion blocking and some curare–like actions in a variety of the experimental animals. On the other hand, xylopinine was described to show the centrally sedative effect with the moderately strong and long–lasting adrenergic alpha–blocking property.[8-10] Although the hypotensive effect of xylopinine in rabbit, cat and dog was shown to be responsible for its adrenergic mode of action, no information was presented on the responses of the heart to xylopinine. In the present experiments, therefore, the effects of xylopinine on the rhythmical contraction of

1) Location: *Yamashina, Higashiyama-ku, Kyoto.*
2) J. Schmutz, *Helv. Chim. Acta,* **42,** 335 (1959).
3) M. Tomita and T. Nakano, *Chem. Pharm. Bull.* (Tokyo), **5,** 10 (1957).
4) M. Tomita and J. Kunitomo, *Yakugaku Zasshi,* **80,** 880 (1960); *ibid.,* **80,** 885 (1960).
5) S. Oyaizu, *Folia Pharmacol. Japon.,* **54,** 1903 (1958).
6) S. Oyaizu, *Folia Pharmacol. Japon.,* **54,** 1106 (1958).
7) K. Shimamoto, M. Fujiwara, and H. Torii, *Folia Pharmacol. Japon.,* **58,** 138 (1962).
8) H. Nakanishi, *Jap. J. Pharmacol.,* **12,** 208 (1962).
9) H. Yamamoto, *Jap. J. Pharmacol.,* **13,** 230 (1963).
10) H. Nakanishi, *Jap. J. Pharmacol.,* **14,** 317 (1964).

the isolated guinea–pig's atria were studied in an attempt to analyse the mechanism of its adrenergic action.

I   II   III : R=CH₃, R'=H
                       IV : R=H, R'=CH₃

III : R=CH_3, R'=H
IV : R=H, R'=CH_3
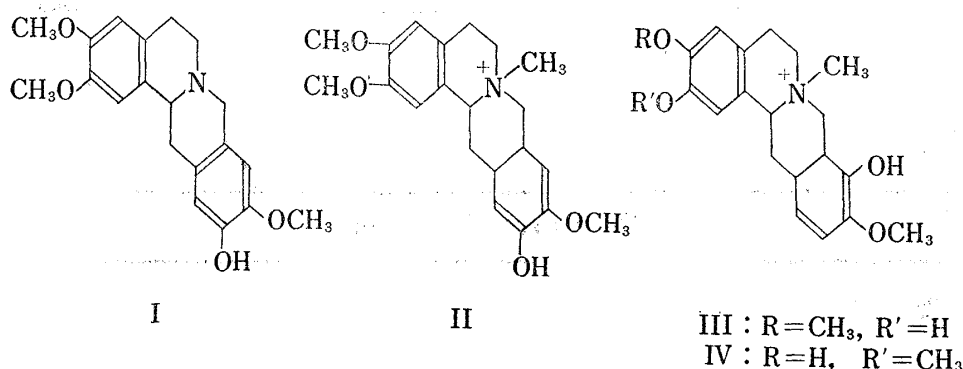
Experimental

The adult guinea–pigs of either sex, weighing 200 to 400 g, were sacrificed through haemorrhage by cutting both carotid arteries. Immediately thereafter, the total heart was isolated and the atrial preparation was made in the fully oxygenated Ringer–Locke solution. The spontaneous contraction of the preparation, suspended in the oxygenated Ringer–Locke solution at the temperature of 30±1°, was recorded on the smoked drum *via* a spring–lever and magnified about 7 times.

The various concentration of xylopinine hydrochloride, *l*-adrenaline hydrochloride and *dl*-isopropylnoradrenaline hydrochloride were administered into the nutrient solution in the organ bath at the full stabilization of the spontaneous contraction of the preparation about one hour after the setting–up. The concentration of all drug in the organ bath was expressed as g/ml. The rates of the atrial beats were counted at 1,3,5 and 7 minutes after the administration until one hour. The effect of drug was usually observed in 5 to 8 preparations and the mean changes of the rate and amplitude of the contraction to the previous rate and amplitude were expressed as the percent change.

Results

I.   Effects of Adrenaline and Isopropylnoradrenaline

The concentration of adrenaline above 10^{-8} produced the positive inotropic and chronotropic effects on the atria. In contrast to the inotropic effect, the positive chronotropic effect showed the excellent dose–response relationship. The percent increases of the spontaneous rate at 1 and 3 minutes after the administration caused by 10^{-8}, 10^{-7} and 10^{-6} of adrenaline were 4.0:7.0, 29.0:38.0 and 38.0:51.0, respectively, on the other hand, by 10^{-8}, 2×10^{-8} and 10^{-7} of isopropylnoradrenaline were 14.0:26.0, 23.0:42.0 and 36.0:47.0, respec-
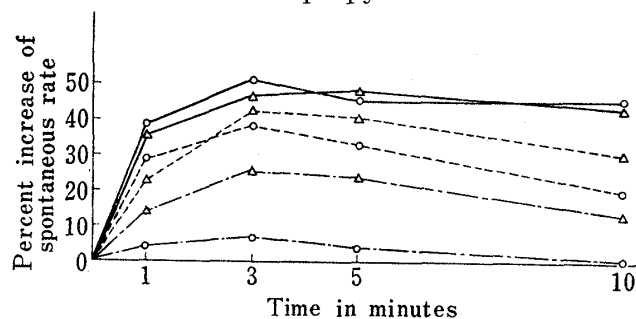

Fig. 1. Percent Increase of Spontaneous Heart Rate of Guinea–pig's Atria by Adrenaline (ad.) and Isopropylnoradrenaline (isup.)

O————O ad. HCl 10^{-8} g/ml
O————O ad. HCl 10^{-7} g/ml
O————O ad. HCl 10^{-6} g/ml
△————△ isup. HCl 10^{-8} g/ml
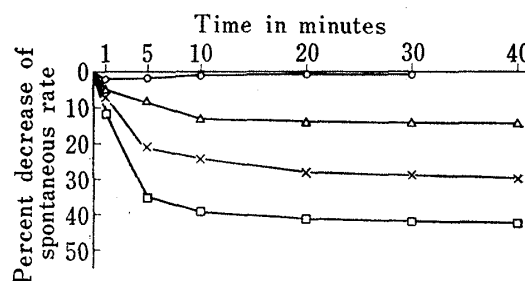△————△ isup. HCl 2×10^{-8} g/ml
△————△ isup. HCl 10^{-7} g/ml

Fig. 2. Percent Decreae of Spontaneous Heart Rate of Guinea–pig's Atria by Xylopinine (xyl.)

O————O xyl. HCl 10^{-7} g/ml
△————△ xyl. HCl 10^{-6} g/ml
×————× xyl. HCl 10^{-5} g/ml
□————□ xyl. HCl 3×10^{-5} g/ml

tively. The peak increase of the rate usually at 3 minutes was followed by the gradual declination to the previous level. The increase of the rate caused by the submaximal concentration of adrenaline and isopropylnoradrenaline were dose dependent and the latter was 5 to 10 times more effective than the former. The results are shown in Fig. 1.

II. Effects of Xylopinine

The spontaneous rate was decreased gradually but progressively by the effective concentrations of xylopinine almost without affecting the amplitude of the concentration. However, the reduction of the rate by the threshold concentration of 10^{-8} to 5×10^{-8} was transient and lasted for about 3 minutes. The percent decreases of the spontaneous rate caused by 10^{-7}, 10^{-6} and 10^{-5} of xylopinine at 1, 10 and 20 minutes after the administration were 3.0:2.0:1.0, 6.0:14.0:15.0 and 7.0:25.0:29.0, respectively (Fig. 2). However, the mean reduction of the rate by 30.0% at 30 minutes after the administration of 10^{-5} of xylopinine was associated sometimes with a slight depression of the amplitude. A significant depression of the amplitude caused by the further increase in concentration of xylopinine recovered gradually from about 15 minutes after the administration. The washingout procedure of the preparation restored promptly the decreased rate to the previous level.

III. Effects of Xylopinine on the Responses of the Atria to Catecholamines

The combined simultaneous administration of 10^{-5} of xylopinine and 10^{-7} of adrenaline produced the mean percent reductions of the spontaneous rate of increase by 8.0, 16.0, 16.0 and 9.0 at 1,3,5 and 10 minutes after the administration, compared with the effects of 10^{-7} adrenaline only. Comparing the effects of the respective agents in the same concentrations, the significant antagonism in the effects on the spontaneous rate was presented between both agents. However, in the presence of 10^{-5} of xylopinine the concentration of 10^{-7} of adrenaline exerted the definitely marked positive inotropic and chronotropic effects on the depressed atria. The comparison of the positive chronotropic effects of adrenaline to the previous levels in the intact and depressed atria, as shown in Fig. 3, indicates that the previous treatment of the atria with the depressing concentration of xylopinine activates significantly the rate-increasing effect of adrenaline. Besides, the depressive concentration of xylopinine did not interfere with the manifestation of the positive inotropic effect of adrenaline. However, the positive chronotropic effect of 10^{-7} of adrenaline, administered immediately after treatment with 10^{-5} of xylopinine was usually less than that of adrenaline before the
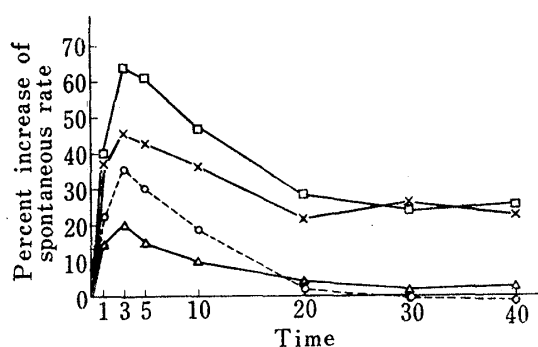
Fig. 3. Percent Increase of Spontaneous Heart Rate of Guinea–pig's Atria by Adrenaline (ad.) under the Influences of Xylopinine (xyl.)

O------O ad. HCl 10^{-7} g/ml
△——△ ad. HCl 10^{-7} g/ml simultaneously with xyl. HCl 10^{-5} g/ml
×——× ad. HC. 10^{-7} g/ml 5 minutes after xyl. HCl 10^{-5} g/ml
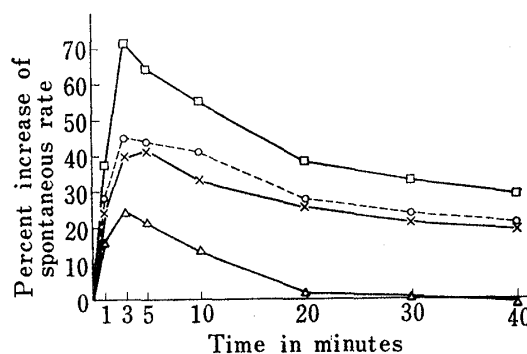□——□ ad. HCl 10^{-7} g/ml 10 minutes after xyl. HCl 10^{-5} g/ml

Fig. 4. Percent Increase of Spontaneous Heart Rate of Guinea–pig's Atria by Isopropylnoradrenaline (isup.) under the Influences of Xylopinine (xyl.)

O-----O isup. HCl 2×10^{-8} g/ml
△——△ isup. HCl 2×10^{-8} g/ml simultaneously with xyl. HCl 10^{-5} g/ml
×——× isup. HCl 2×10^{-8} g/ml 5 minutes after xyl. HCl 10^{-5} g/ml
□——□ isup. HCl 2×10^{-8} g/ml 10 minutes after xyl. HCl 10^{-5} g/ml

treatment with xylopinine. This evidence indicates also that xylopinine have two mutually opposite effects on the positive chronotropic response of the atria to adrenaline.

The effects of xylopinine on the chronotropic response of the atria to isopropylnoradrenaline resembled closely with those on the same response to adrenaline. Xylopinine and isopropylnoradrenaline proved to be mutually antagonistic on the spontaneous rate when both agents were administered simultaneously. However, in contrast to the significant depression of the positive chronotropic effect of the amine at the early phase of the atrial depression, the same effect of the amine was significantly potentiated at the late phase of the atrial depression caused by xylopinine, as shown in Fig. 4. The positive inotropic effect of isopropylnoradrenaline was not affected by the treatment of the atria with the depressive concentration of xylopinine as well.

Discussion

The long-lasting and relatively strong adrenergic alpha-blocking effect of xylopinine has been confirmed on the blood pressure of rabbit, cat and dog by Nakanishi.[8] In the present experiments the effects of xylopinine on the spontaneous contraction of the isolated guinea-pig's atria and the responses of the organs to adrenaline and isopropylnoradrenaline were observed. Xylopinine in the concentration above 10^{-8} depressed the rate of the spontaneous beat without affecting the amplitude of the contraction. However, some depression of the contraction was observed in the concentration above 10^{-5}. No abolition of the spontaneous beat was attained by the higher concentrations. The depression of the spontaneous beat by xylopinine was easily reversed by washing-out of the preparation.

The chronotropic responses of the atria to adrenaline and isopropylnoradrenaline were more reliable to the doses than the inotropic responses. Adrenaline was less in intensity and duration in the chronotropic effect than isopropylnoradrenaline. The introduction of the adrenergic beta-blocking agents such as dichlorisopropylnoradrenaline, pronethalol and propranolol into the experimental pharmacology has established[11] that the positive inotropic and chronotropic effects on the heart are due to the stimulation of the adrenergic beta-receptors. The previous treatment of the atria with the depressing concentrations of xylopinine on the atrial beat exerted the biphasic effects on the positive chronotropic responses to catecholamines, the early antagonism and the late potentiation.

From the fact that xylopinine has the adrenergic alpha-blocking property,[8-10] it is reasonable to assume the late potentiation is derived from the blocking of the alpha-receptor by xylopinine, and the resultantly dominant manifestation of the beta-receptor activity, but on the other hand, the fact that no significant difference in the potentiating effect between adrenaline with considerable alpha-receptor stimulating effect and isopropylnoradrenaline with no such effect may indicate the lack of the adrenergic alpha-receptor in the atria. Therefore, it is much likely that if the atria is enough sensitive to the catecholamine, the increase of the rate is usually more marked when the previous rate is decreased than when the previous rate is intact. If this assumption was allowed, the antagonism between xylopinine and catecholamine in the effect on the atrial rate is concluded to be derived from the non-specifically decreased sensitivity of the atria to the amines.

11) J.R. Blinks, *Ann. N. Y. Acad. Sci.*, **139**, 673 (1967).