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THE CONTRACTIVE MECHANISM OF NICOTINE IN ISOLATED AORTA OF RABBITS, WITH SPECIAL REFERENCE TO CATECHOLAMINE RELEASE

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Indexing Words

nicotine; tyramine; noradrenaline; cross-tachyphylaxis; isolated aorta of rabbits

Aritomo SUZUKI, Toshihiko FUNASAKA and Hiroshi MATSUMOTO. *The Contractive Mechanism of Nicotine in Isolated Aorta of Rabbits, with Special Reference to Catecholamine Release.* Kobe J. Med. Sci. 19, 111-125, September 1973——There are a lot of reports that nicotine has the indirect action through catecholamine release. But these reports only describe the fact that nicotine has the action of catecholamine release. We investigated the mechanism of catecholamine release of nicotine in detail, especially comparing with that of tyramine.

INTRODUCTION

An attempt has been focussed to the fact that nicotine (Nic) has the indirect action through catecholamine (CA) release from sympathetic nerve ending in some organs, in addition to the well-known autonomic nerve ganglion stimulation (followed by paralysis): That is, the action of CA release of Nic in the intestines,[7, 16, 28] trachea,[18] adrenal gland,[12, 40] heart[6, 15, 25, 29, 30] and blood vessels[8, 9, 17, 27, 35, 43, 48] is noticed. This action of Nic in the blood vessels has been reported on rabbits' ear vessels (Ginzel et al.[17] and Burn et al.[9]) and rabbits' aortae (Millson[35], Burn et al.,[8] Watanabe[48] and Setnikar et al.[43]). These reports, however, do not fully describe the detailed mechanism of CA release of Nic. It is said[42] that depolarization of the nerve cell membrane preceeds in CA release of Nic, but there still remains obscure the information about the CA store site which will be released by Nic.

For the purpose of studying the phenomenon of CA release and its release mechanism which participates in the Nic contraction, the present study deals with the effect of various drugs on the contractions of Nic, tyramine (Ty) and noradrenaline (NA) in the isolated aortic strip of rabbits, especially by comparison with the mechanism of CA release of Ty. In addition, some accopmanying experiments related to these were performed. The results obtained are reported below. The reason why the NA contraction was included in this comparison was to ascertain that the change of every contractions of Nic, Ty and NA is due to the change of CA release which interposes in the process of these actions and not due to the secondary change caused by the change of the NA action.

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MATERIALS AND METHODS

According to Watanabe[48] and Furchgott,[14] rabbits were killed by cutting the bilateral carotid arteries, and isolated ascending aorta was spirally cut (about 2 cm in length and 5 mm in width) after the removal of adherent fat tissue. Then the preparation was suspended in Magnus apparatus and allowed to stretch for at least 2^h prior to adminstration of drugs, and tonus was recorded on the smoked drum. About 1.8 g was loaded on a lever, and the rate of magnification of the change of tonus was about 17-fold. The Locke solution (NaCl 9.0 g, KCl 0.42 g, $CaCl_2$ 0.24 g, glucose 1.0 g, $NaHCO_3$ 0.4 g/l, pH 7.2-7.4) was used for bath fluid, which was constantly kept at 35 °C and aerated with a pump. The concentrations of the contracting drugs, NA, Ty and Nic used in the experiment to investigate the influence by various drugs (combined drugs) were 10^{-8} to 10^{-7}, 2×10^{-5}, 10^{-5} to 2×10^{-5} respectively, and the contractions caused by these concentrations showed the height of about 50 to 70% of the maximal contraction. The repeated application of these contractions (at intervals of 30 to 60^m) did not cause tachyphylaxis in the case of NA, and in the case of Nic and Ty the tachyphylaxis was mostly not so clear or appeared only slightly, if any. Thus, there was no disturbance in judging the influences of combined drugs.

A combined drug was applied 10^m prior to the application of an active drug (except for a case of reserpine used for CA depletion). The concentration of an combined drug used was inactive in itself, so that a combined effect of algebraic sum might be excluded in the drug interactions tested.

Since the repeated application of the high concentration of Nic (5×10^{-5} to 10^{-4}) or that of Ty (5×10^{-5} to 10^{-4}) produced the remarkable tachyphylaxis, these concentrations were used in the experiment for the study of tachyphylaxis of Nic and Ty.

Drugs used are as follows:

Noradrenaline hydrochloride (Sankyo), tyramine hydrochloride (Sigma), nicotine (Tokyo Kasei), yohimbine hydrochloride (Ono), dihydroergotamine methansulfonate (Sandoz), pyrogallol (pyrogallic acid, Hirose), catron (β-phenylisopropyl hydrazine hydrochloride) (Chugai), hexamethonium bromide (Yamanouchi), mecamylamine hydrochloride (Meiji), pendiomide bromide (Ciba), bretylium tosylate (Chugai), guanethidine sulfate (Ciba), ethylendiamine tetraacetic acid disodium (EDTA-2 Na) (Hirose).

RESULTS

I. Influence of the various drugs on the contractions of nicotine, tyramine and noradrenaline.

The experimental results obtained are summarized in Table 1.

1. Influence of sympathetic α-blocking drugs.

a) Influence of yohimbine.

The minimal inhibitory concentrations of yohimbine (Y) to noradrenaline (NA),

Table 1 Influence of various drugs on the contractions of noradrenaline, tyramine and nicotine.

	Noradrenaline	Tyramine	Nicotine
Yohimbine	↓ (10^{-7})	↓ (10^{-7})	↓ (10^{-7})
Dihydroergotamine	↓ (10^{-8})	↓ (2×10^{-8})	↓ (5×10^{-8})
Pyrogallol	↑ (10^{-7})	↑ (10^{-7})	↑ (10^{-7}) ↓ (10^{-5})
Catron	↑ (2×10^{-7})	↑ (2×10^{-5})	↑ (2×10^{-5})
Reserpine (Catecholamine depletion)	—	↓ (卅)	↓ (卅)
Cocaine	↑ (10^{-6})	↓ (10^{-6})	↓ (10^{-6})
C_6	— (10^{-4})	— (10^{-4})	↓ (10^{-6})
Mecamylamine	— (10^{-5})	— (10^{-5})	↓ (10^{-7})
Pendiomide	— (5×10^{-4})	—(5×10^{-4})	↓ (10^{-6})
EDTA-2 Na (Ca removal from medium	↓ (+)	↓ (卄)	↓ (卅)
Guanethidine	— (10^{-5})	↓ (10^{-6})	↓ (2×10^{-6})
Bretylium	—or ↑ (10^{-5}) ↓ (10^{-4})	↓ (10^{-6})	↓ (5×10^{-6})

↑ increase, ↓ decrease, — no influence.

tyramine (Ty) and nicotine (Nic) were equally 10^{-7} respectively (Table 1). The degree of inhibition was strengthened in accordance with the increase of the Y concentration, and Y of the high concentration (10^{-5} to 2×10^{-5}) completely inhibited the contractions of these three contracting drugs (Fig. 1).

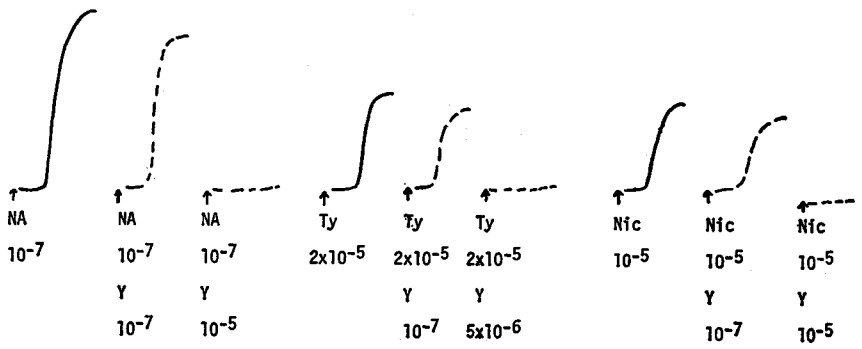

Fig. 1 Influence of yohimbine (Y) on the contractions of noradrenaline, tyramine and nicotine.

b) Influence of dihydroergotamine.

The minimal inhibitory concentrations of dihydroergotamine (DHE) to NA, Ty and Nic were almost the same showing about 10^{-8}, 2×10^{-8} and 5×10^{-8} respectively; a little higher concentration was required for NA, Ty and Nic in ascending order (Table 1). As in the case of Y, DHE of the high concentration (2×10^{-6} to 5×10^{-5}) completely inhibited the contractions of NA, Ty and Nic (Fig. 2).

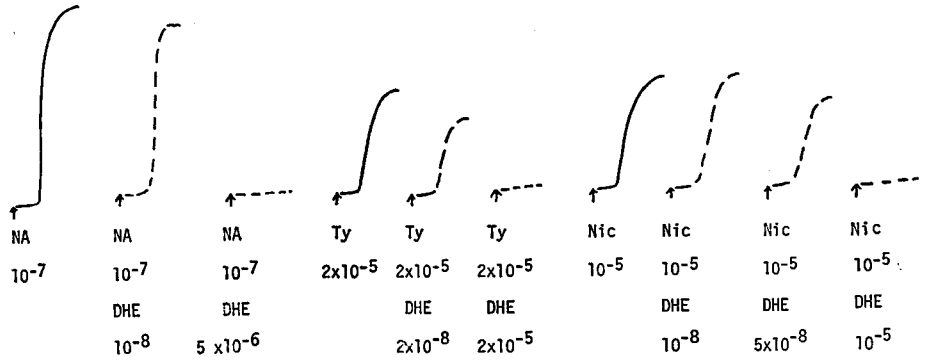

Fig. 2 Influence of dihydroergotamine (DHE) on the contractions of noradrenaline, tyramine and nicotine.

2. *Influence of pyrogallol (catechol-O-methyltransferase inhibitor).*

Pyrogallol (Py) increased the contractions of NA, Ty and Nic from almost the same concentration (10^{-7}). But Py of the high concentration (10^{-5}) potentiated the contractions of NA and Ty, inhibiting slightly the Nic contraction (Table 1 and Fig. 3).

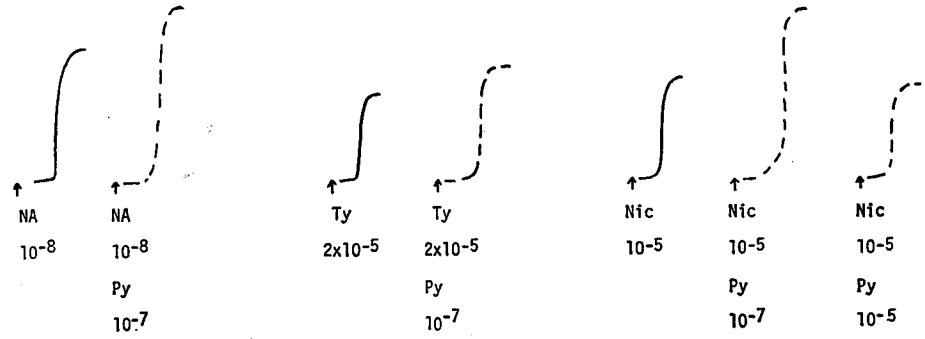

Fig. 3 Influence of pyrogallol (Py) on the contractions of noradrenaline, tyramine and nicotine.

3. *Influence of catron (monoamine oxydase inhibitor).*

Catron potentiated the contractions of NA, Ty and Nic from the same concentration (2×10^{-5}) (Table 1 and Fig. 4).

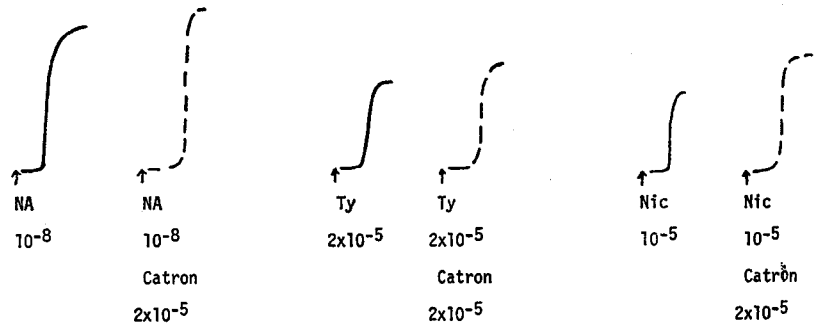

Fig. 4 Influence of catron on the contractions of noradrenaline, tyramine and nicotine.

4. Influence of reserpine (catecholamine depletion).

According to Watanabe,[48] the preparation was exposed to the high concentration (10^{-5}) of reserpine for 30^{m} and then washed out repeatedly. By this procedure, the Ty and Nic contractions were remarkably inhibited, and especially the Ty contraction was abolished in some cases, while no influence on the NA contraction was produced. After the NA repletion (10^{-5} for 20^{m}, then wash out) was performed on the preparation in which the Ty or Nic contraction was remarkably recovered by the same procedure, the Ty and Nic contractions were remarkably recovered, especially the recovery of Ty contraction was larger than that of Nic (Table 1 and Fig. 5).

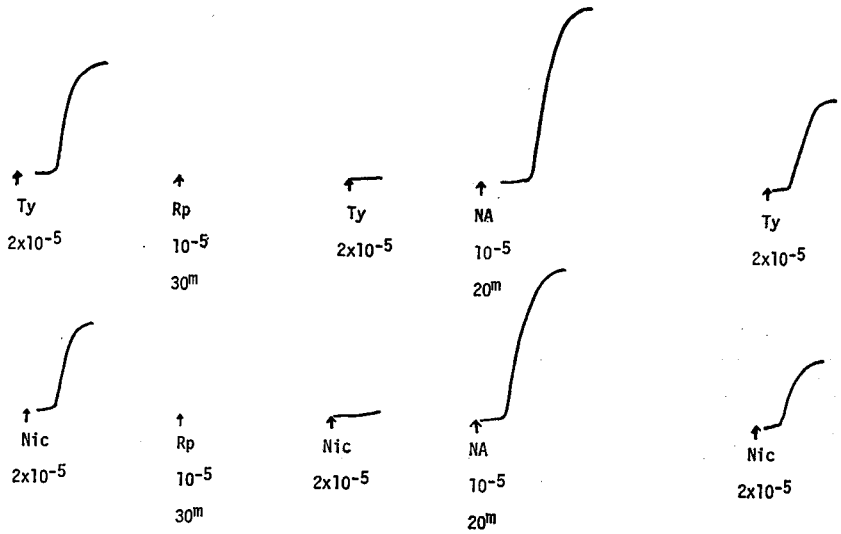

Fig. 5 Influence of reserpine 10^{-5}, 30^{m} (catecholamine depletion) and its removal by noradrenaline repletion (noradrnailne 10^{-5}, 20^{m}).

5. Influence of cocaine.

The NA contraction was potentiated by cocaine of the concentrations of 10^{-6} to 5×10^{-6}, while the Ty and Nic contractions were inhibited from the concentration of 10^{-6} and strongly inhibited at the high concentration (5×10^{-6}) (Table 1 and Fig. 6).

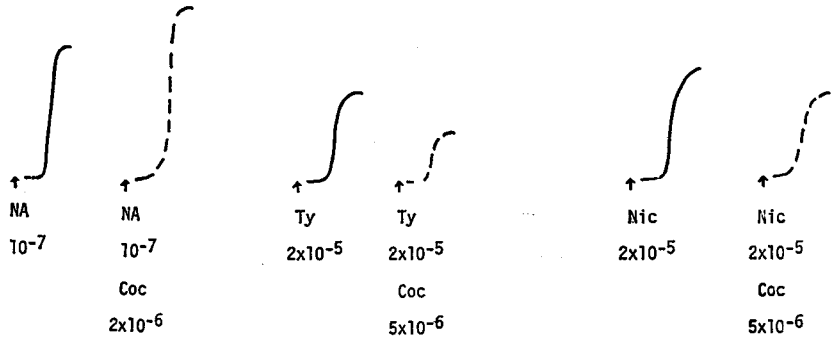

Fig. 6 Influence of cocaine on the contractions of noradrenaline, tyramine and nicotine.

6. Influence of EDTA-2 Na (removal of Ca from bath fluid).

The NA contraction was slightly inhibited by EDTA-2 Na of the concentration of 5×10^{-4} or 10^{-3}, and the Ty contraction was inhibited much stronger than that of NA; it is not disappeared, however. On the other hand, the Nic contraction was reduced much stronger than that of Ty, and completely disappeared. About thirty minutes after the bath solution was exchanged from normal Locke solution to the Ca free solution, the influence observed on the contractions of NA, Ty an Nic were the same as observed on that of EDTA-2 Na (Table 1 and Fig. 7). From these results, it is conceivable that the EDTA action exerts the effect which corresponds to the removal of Ca from the medium.

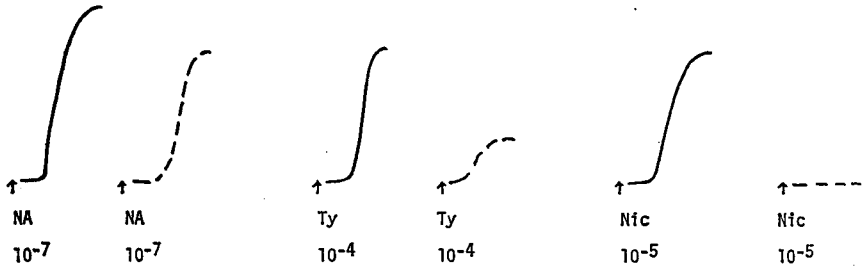

Fig. 7 Influence of Ca removal from the bath solution on the contractions of noradrenaline, tyramine and nicotine. Solid line: normal bath solution, broken line: modified bath solution.

7. Influence of bretylium.

Bretylium (Br) inhibited the Ty and Nic contraction from the concentration

of 10^{-6} and 5×10^{-6} respectively. At the concentration of 10^{-5} Br had no influence on the NA contraction in many cases, though showed the increase in some samples, showing the antagonism in all cases at the high concentration (10^{-4}) (Table 1 and Fig. 8).

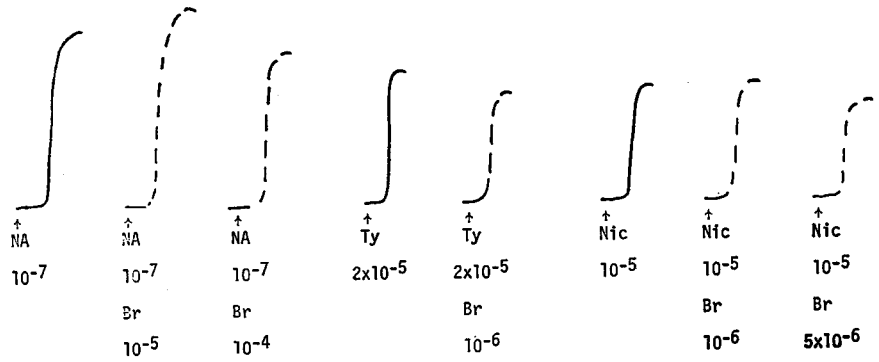

Fig. 8 Influence of bretylium on the contractions of noradrenaline, tyramine and nicotine.

8. Influence of guanethidine.

Guanethidine inhibited the contractions of Ty and Nic from the concentration of 10^{-6} and 2×10^{-6} respectively. The NA contraction was slightly inhibited by the 10^{-5} concentration of guanethidine in very few cases, but almost uninfluenced (Table 1).

9. Influence of ganglion blocking agents.

a) Influence of C_6.

C_6 inhibited the Nic contraction from the 10^{-6} concentration and showed almost the complete inhibition at the 10^{-5} concentration, while the NA and Ty contractions were not affected even by the high concentration (10^{-5}) of C_6 (Table 1 and Fig. 9).

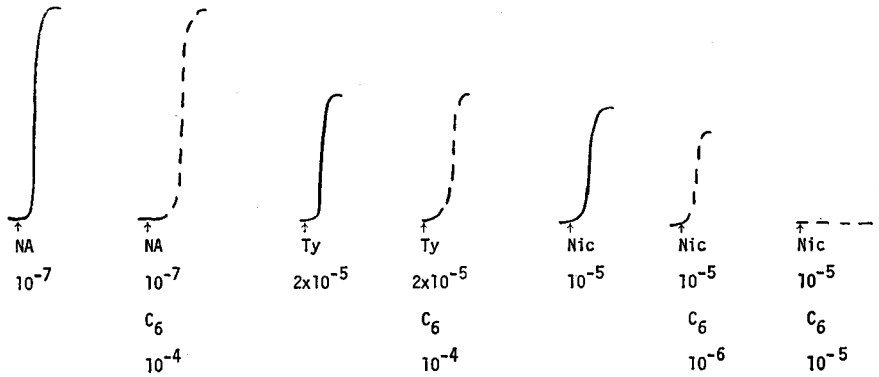

Fig. 9 Influence of C_6 on the contractions of noradrenaline, tyramine and nicotine.

b) Influence of mecamylamine.

Mecamylamine inhibited the Nic contraction from the 10^{-7} concentration and completely inhibited at the high concentration (10^{-5}). The NA and Ty contractions were not affected even by the high concentration (10^{-5}) of mecamylamine (Table 1 and Fig.10).

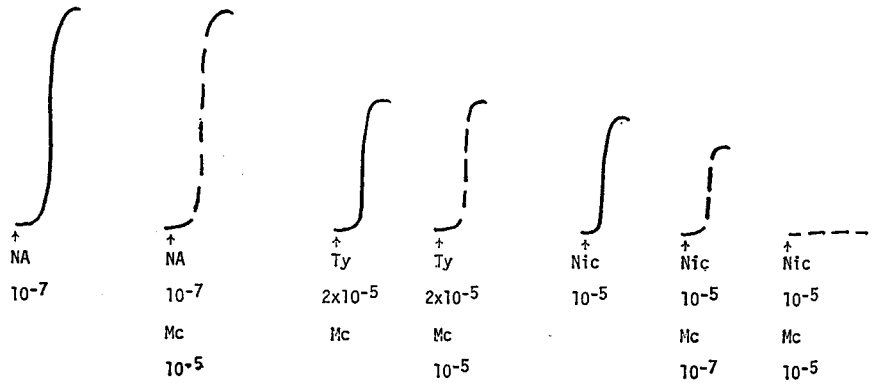

Fig. 10 Influence of mecamylamine on the contractions of noradrenaline, tyramine and nicotine.

c) Influence of pendiomide.

Pendiomide inhibited the Nic contraction from the 10^{-6} concentration and completely inhibited at the 10^{-4} concentration. However, the contractions of NA and Ty were not affected even by the high concentration (5×10^{-4}) of pendiomide (Table 1 and Fig. 11).

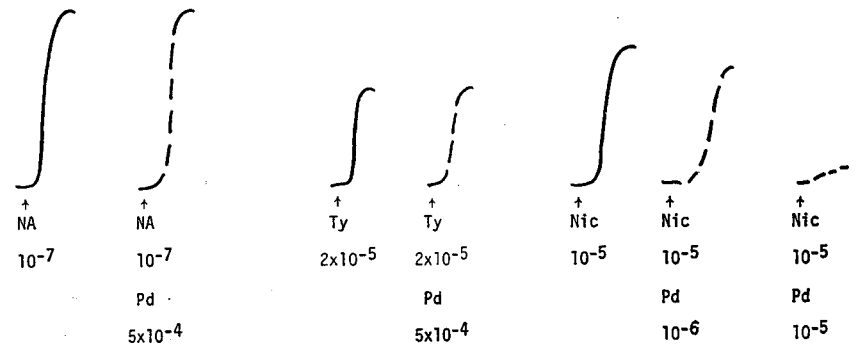

Fig. 11 Influence of pendiomide on the contractions of noradrenaline, tyramine and nicotine.

II. Experiments on the tachyphylaxis of tyramine and nicotine.

1. Tyramine tachyphylaxis.

By the repeated application (at intervals of 15 to 30^{m}) of Ty of the high concentration (5×10^{-5} to 10^{-4}), the Ty contraction was in many cases gradually decreased and finally disappeared. That is, the remarkable tachyphylaxis was observed. So-called NA repletion (10^{-5} for 20^{m}, then wash out) to the preparation in which tachyphylaxis was produced remarkably recovered the Ty contraction (Fig. 12-A). The co-existence of Ty of the high concentration with the NA repletion inhibited the recovery of the Ty contraction (Fig. 12-B), but the co-existence of Nic of the high concentration (10^{-4}) did not inhibit the recovery of the contraction (Fig. 12-C).

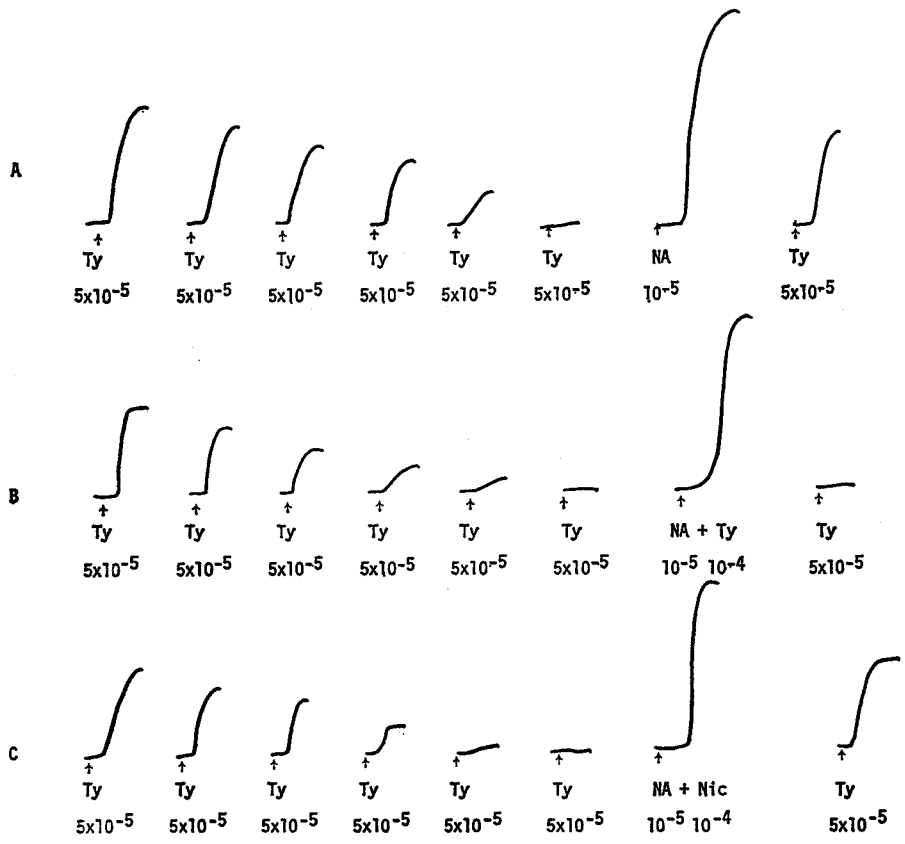

Fig. 12 Influence of tyramine and nicotine on the repleting effect of noradrenaline (10^{-5}, 20^{m}) after the tyramine tachyphylaxis.

2. *Nicotine tachyphylaxis.*

By the repeated application (at intervals of 10 to 30^{m}) of Nic of the high concentration (5×10^{-5} to 10^{-4}) the Nic contraction was gradually reduced and finally disappeared; that is, the remarkable tachyphylaxis was observed. The Nic contraction abolished by tachyphylaxis was not recovered by the NA repletion at all, differing from the case of Ty tachyphylaxis (Fig. 13).

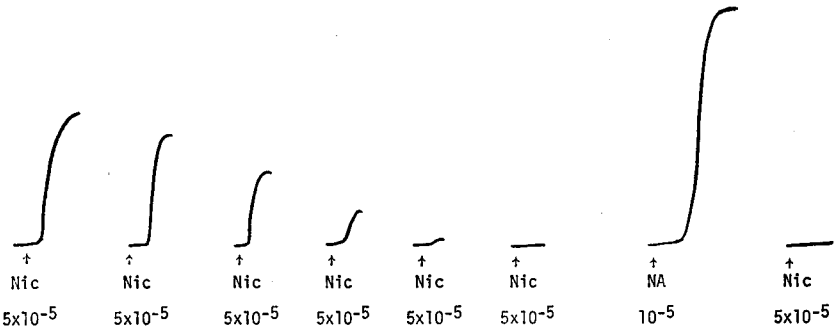

Fig. 13 Influence of noradrenaline incubation (10^{-5}, 20^{m}) on the nicotine-tachyphylaxis.

3. *On the existence of cross-tachyphylaxis between tyramine and nicotine.*

The Nic contraction was strongly inhibited in the preparation in which the Ty contraction was previously abolished by the repeated application of Ty of the high concentration (5×10^{-5} to 2×10^{-4}); that is, the phenomenon of cross-tachyphylaxis was observed. However, the Nic contraction still existed slightly (Fig. 14-A). On the other hand, in the preparation in which the Nic tachyphylaxis was produced by the repeated application of Nic of the high concentration (5×10^{-5} to 10^{-4}), no change was observed in the Ty contraction (Fig. 14-B). That is, unilateral cross-tachyphylaxis was observed between Ty and Nic.

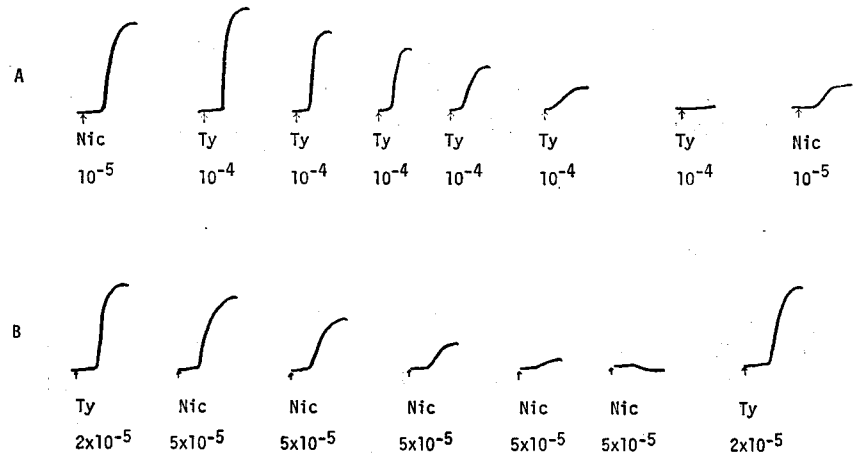

Fig. 14 Cross-tachyphylaxis tested between tyramine and nicotine.

DISCUSSION

From the fact that the Nic contraction in rabbit aorta was inhibited by sympathetic α-blocking agents, yohimbine and dihydroergotamine from almost the same concentration as well as the contraction of NA or Ty and abolished at the high concentration, it is conceivable that the Nic contraction is due to the stimulation of adrenergic α-receptor, and that the other mechanism do not participate in the Nic contraction. According to Millson,[34] the sympathetic blocking agents have the tendency to antagonize against exogenous CA more easily than against endogenous CA, which might be the reason why the minimal inhibitory concentration of dihydroergotamine to Ty and Nic was slightly higher (twice to five-fold) than that to NA.

Considering the following results, it may be suggested that the stimulating action of adrenergic receptor of Nic is indirect through the CA release: 1) The Nic contraction, as well as the Ty contraction, was remarkably reduced by the pretreatment with resrpine (Rp) which depletes CA from the store. 2) Like the Ty contraction, the Nic contraction was remarkably inhibited by cocaine which inhibits the CA release from the store. 3) The Nic contraction was potentiated by pyrogallol, catechol-O-methyltransferase inhibitor as well as the Ty and NA contractions. And 4) the Nic contraction, as well as the NA and Ty contractions, was potentiated by catron, monoamine oxydase inhibitor.

According to the literatures[3, 10, 13, 14, 20, 21, 28, 32, 34, 39, 41, 44, 45, 49] there are at least two kinds of CA store; one is so-called Ty sensitive store containing the CA released by Ty, and the other is the store containing the CA released by sympathetic nerve stimulation. It is said that cocaine strongly inhibits the CA release by Ty but weakly inhibits the CA release by nerve stimulation, or rather potentiates the CA release (it is said[2, 19, 22, 27, 31, 33, 36, 37, 46, 47, 50] that this potentiation is due to the inhibition of reuptake of released CA into the CA store). Considering these findings and the results obtained by the authors, the comparison between the mechanism of CA release by Nic and that by Ty was carried out, and the following observation was obtained.

Compared the Nic contraction with the Ty contraction as to the effect of various drugs, it was found that there existed both the similarity and difference between them. The former was that 1) the Nic and Ty contractions were inhibited by cocaine to almost the same degree, 2) the minimal inhibitory concentrations of bretylium or guanethidine to Nic and Ty were almost the same (it was slightly weaker to Nic than to Ty): According to literatures,[1, 4, 24, 34, 39] it is said that bretylium and guanthidine of the high concentrations inhibit the CA release by Ty, but the CA release by nerve stimulation is preferentially inhibited at much lower concentrations of bretylium and guanethidine. However, the results obtained in the present investigation as to the Nic contraction in the Ty-tachyphylaxis preparation in which the Ty contraction was completely abolished by the repeated application of Ty showed a marked reduction of Nic contraction (but not disappeared). From this fact, it is conceivable that the CA store on which Nic acts may be mainly the Ty sensitive store but it may partly contain the other store, which might be supported by the similarity between the Nic and the Ty contraction stated above. It is also assumed that the store on which Nic mainly acts might be different from the store

on which nerve stimulation acts.

As stated above, it may be thought that Nic mainly releases CA from the Ty sensitive store. However, concerning the detailed mechanism of the CA release, it is suggested that there exists remarkable difference between Nic and Ty by the following results obtained by the authors; that is, 1) in the preparation in which Nic tachyphylaxis was completed, no change was found in the Ty contraction. 2) Ty tachyphylaxis was removed or reduced by the NA repletion, while Nic tachyphylaxis was unaffected by the NA repletion. 3) The removal phenomenon of Ty tachyphylaxis by NA repletion was inhibited by the co-existence of Ty, but not inhibited by that of Nic. And, 4) there were some differences in the influence of drugs. That is, the Nic contraction was inhibited by the ganglion blocking agents (C_6, pendiomide and mecamylamine), but the Ty contraction was not inhibited by the ganglion blocking agents. The removal of Ca from bath fluid inhibited the Nic contraction much stronger than the Ty contraction to make the Nic contraction abolished.

These results might support the well-known viewpoint[11,28,38] that the CA release by Ty is due to the exchange reaction of Ty with CA in the store (not via depolarization of the cell membrane) and that Ty tachyphylaxis is due to the reduction of the movable CA. In addtion, it would be supposed that the mechanism of CA release by Nic may be different from that by Ty: That is, Nic firstly acted on the cell membrane and produced depolarization to release CA through Ca^{++} invading from the outside of cell or released from the cell membrane. This supposition is firmly supported by the fact that Ca^{++} in bath fluid is essential for the Nic contraction. It is clear that the cause of Nic tachyphylaxis is not due to the reduction of the movable CA in store as in the case of Ty, and it may be attributed to the change of the sympathetic nerve cell membrane. Alike the well-known explanation for the stimulation followed by the paralysis of the ganglion cell by Nic, the cause of Nic tachyphylaxis is thought to be due to the reason that depolarization of the sympatheic nerve cell by Nic is not easily removed, being prolonged and thus a new depolarization can not be caused after the repeated application of Nic. On the basis of these suppositions, it may be safely explained without any discrepancy why unilateral cross-tachyphylaxis only was formed between Nic and Ty despite of the genegral supposition that the CA store on which Nic chiefly acts is identical with the CA store on which Ty acts. The fact that the Nic contraction was specifically inhibited by the ganglion blocking agents may be due to the inhibition of depolarization by Nic by competitive antagonism at the Nic receptor on the cell membrane of sympathetic nerve which produces the CA release. If this is the case, it is suggested that there exists in this Nic receptor the similar constitution to the Nic receptor of ganglion.

Considering the difference in the mechanism of CA release between Ty and Nic as stated above, there is much stronger possibility of the difference of the antagonistic mechanism rather than their similarity for the fact that antagonistic activities of cocaine, bretylium and guanethidine against the Ty and Nic contractions were similar; it has been reported[13, 14, 45] that cocaine competitively inhibits the CA release of Ty, but much more attention should be paid to the possibility that the inhibitory action of cocaine on the depolarization of cell membrane may participate in the inhibition of CA release by Nic.

CONCLUSION

The contractive mechanism of nicotine was investigated in aortic strip of rabbits, with speical reference to catecholamine release.

1. The effects of various drugs on the contractions of nicotine, tyramine and noradrenaline were compared with one another and the results obtained were shown in Table 1.

2. After the completion of tyramine tachyphylaxis, the nicotine induced contraction was inhibited strongly (but remained slightly). However, the tyramine induced contraction was unaffected by the completion of nicotine tachyphylaxis.

3. Summarizing the results stated above, the following conclusion was obtained as to the contractive mechanism of nicotine.

1) The nicotine induced contraction is due to the indirect mechanism through the catecholamine release.

2) It is supposed that catecholamine released by nicotine may mainly come from the tyramine sensitive store and partly come from the other stores.

3) Unlike tyramine, catecholamine release by nicotine is not induced by the exchange reaction but via the action of Ca^{++} which starts under the precedence of depolarization of the sympathetic nerve cell membrane.

4) The similarity of nicotine receptor was suggested between the cell membrane of sympathetic nerve which produces catecholamine release and that of autonomic nerve ganglion.

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