Serial studies have been brought about on the nicotine detoxication with special reference to the metabolic fate of nicotine (1-7) and also on the action mechanism of nicotine antagonists (8-12) by Yamamoto and his coworkers since 1951. The fact that thiamine possessed an antagonistic action on nicotine toxicity was firstly pointed out by Unna et al. in 1944 (13) and the present author found also that thiamine inhibited selectively the action of nicotine as well as nornicotine in vitro.

The present experiment was aimed to elucidate the antagonistic mechanism between thiamine and nicotine, and also to investigate the structure-activity relationship of various thiamine related compounds.

METHODS

I. Experiments on excised organs
a) The guinea pig’s excised intestine
The small intestine of a guinea pig bled to death by a cut of bilateral common carotid arteries was immediately excised and suspended in a bath containing 20 ml of aerated Tyrode solution following Magnus’ method at 30±0.5°C. The values of PA, of thiamine and various agents, proposed by Lockett et al. (14), for nicotine, nornicotine, histamine and acetylcholine were evaluated. Changes in nicotine concentration standard curves following addition of thiamine were observed.

b) The rabbit’s ear
Krawkow-Pissemski’s perfusion method was employed with Locke solution as a perfusate and the perfuse volume was measured by dropmeter.

c) The excised toad’s sinoauricle
The excised toad’s sinoauricle preparation following the description by Fukuhara (15) was used.

II. Peripheral effects of thiamine
a) Effects on blood pressure in dogs
Adult dogs weighing about 8 kg were anesthetized with pentobarbital sodium and their arterial blood pressure from the unilateral common carotid artery was recorded on kymograph via mercury manometer.
b) Effects on the contraction of the nictitating membrane in cats

Effects of thiamine on the nictitating membrane of pentobarbital sodium anesthetized cats weighing about 3 kg were observed.

c) Effects on nicotine-induced hyperglycaemia

Adult rabbits and dogs, weighing 2 to 3 kg and 7 to 13 kg respectively were used after a 20 hour fasting. The peripheral blood was taken from the auricular vein of unanesthetized rabbits and the femoral vein of pentobarbital sodium anesthetized dogs, respectively. The blood sugar was estimated on Somogyi’s method.

III. Effects of thiamine on mortality and convulsion induced by nicotine

Mature dd strain mice, 12-18 g in weight, of both sexes were used. LD₅₀, which were calculated from the observed percentage mortality following Litchfield-Wilcoxon’s method, were compared.

The experimental effects of thiamine which had been subcutaneously preadministered on convulsions due to electroshock and chemoshock were also observed in albino rats and mice.

IV. Effects of thiamine on antidiuretic actions

Experimental conditions for the antidiuretic effect of smoking in human beings were as follows: There were tested young adult volunteers, whose initial morning urine was discarded and subsequent urine samples were taken continuously in a volume of 15-30 ml at intervals of 15 minutes. They were to drink 600 ml of water within 5 minutes intervals. Five minutes after they urinated a volume over 50 ml, they were to smoke within two minutes a cigarette (Japanese “Peace” brand) from seven to three centimeters in length. In other experiments, intravenous injection of 100 mU of a pituitary posterior hormone, Atonin (Nippon Zoki Ltd.), instead of smoking was likewise given 5 minutes after the urine volume reached over 50 ml. Thiamine was also injected intravenously at dosages of 50, 100 and 200 mg immediately after the urine volume reached over 50 ml.

V. Effects of thiamine related compounds on nicotine-induced contractions of the excised small intestine

Following Magnus’ method, experiments were performed on the excised rabbit and guinea pig intestines as mentioned in I. The compounds tested were added to a bath containing 20 ml of aerated Tyrode solution two minutes before the addition of 10 µg of nicotine.

RESULTS

I. Experiments on excised organs

a) The guinea pig’s excised intestine

A marked contraction of the small intestine occurred after 20 µg of nicotine was put into the bath. While the addition of 200 µg of thiamine to 20 µg of nicotine did not result in any inhibition of contraction, the addition of 2 mg of thiamine to the same dose of nicotine led to a slight inhibition of contraction. The contraction induced
by 20 μg of nicotine was almost completely inhibited following the addition of 4 mg of thiamine.

An attempt was made to pursue the specificity of the antinicotine action of thiamine in reference to the mode of action.

The nicotine concentration standard curve was observed to shift to the right side in parallel with the original curve following a pretreatment with graded doses of thiamine (Fig. 1). As a result, the standard curve of nicotine concentration following administration of thiamine showed the so-called competitive antagonism.

The values of PA₂ of several pharmacologically related compounds for nicotine, nornicotine, histamine and acetylcholine in excised guinea pig's intestines were evaluated (Table 1). That is, thiamine showed the largest value for nicotine revealing a similarity to nornicotine of which pharmacological action was already reported by Kitamura (16), one of my colleagues, to be essentially the same as the action of nicotine.

![FIG. 1. Changes in nicotine concentration standard curves following administration of thiamine.](image-url)

**TABLE 1.** PA₂ values to nornicotine, histamine and acetylcholine.

<table>
<thead>
<tr>
<th></th>
<th>Nornicotine</th>
<th>Nicotine</th>
<th>Histamine</th>
<th>Acetylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracethlammonium bromide</td>
<td>4.2</td>
<td>4.5</td>
<td>&gt;3.3</td>
<td>&gt;3.3</td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>5.6</td>
<td>5.4</td>
<td>&gt;2.5</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>6.2</td>
<td>6.3</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>5.7</td>
<td>5.9</td>
<td>8.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Chlorpromazine sulfoxide</td>
<td>4.9</td>
<td>4.9</td>
<td>6.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Dipercol</td>
<td>5.8</td>
<td>5.8</td>
<td>7.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Thiamaine</td>
<td>5.8</td>
<td>5.9</td>
<td>&gt;2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>2,4-Diamino-5-phenylthiazole</td>
<td>4.4</td>
<td>4.5</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>2-Amino-4-methyl-5-phenylthiazole</td>
<td>5.0</td>
<td>5.0</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td>2-Amino-4-phenylthiazole</td>
<td>4.3</td>
<td>4.3</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Atropine</td>
<td>7.5</td>
<td>7.5</td>
<td>5.8</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Excised guinea pig intestine used following Magnus' method at 30°C.
The above agents administered 2 minutes before administration of nornicotine, nicotine, histamine and acetylcholine respectively.
THIAMINE AS NICOTINE ANTAGONIST

b) The rabbit's ear

Rabbit ear vessels were markedly contracted following administration of nicotine. Two hundred micrograms of thiamine showed no influences upon the contraction induced by 20 μg of nicotine, and an increase in the dosage of thiamine showed an inhibition of contraction. Two milligrams of thiamine completely antagonized the contracting action shown by 20 μg of nicotine.

c) The excised toad's sinoauricle

Administration of 20 μg of nicotine showed a marked decrease in the amplitude of contraction followed by a slight increase.

It was concluded that the antinicotinic action of thiamine was not attributable to a mere chemical antagonistic factor considering a wide ranged variation of antagonistic ratio of thiamine against nicotine which was observed depending upon the kind of excised organs used (Table 2).

Table 2. Antagonistic ratios of thiamine against nicotine on excised organs.

<table>
<thead>
<tr>
<th>Kind</th>
<th>Nicotine dose (μg)</th>
<th>Complete blocking doses of thiamine for the action of nicotine (mg)</th>
<th>Thiamine dose Nicotine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraction of excised guinea pig small intestine</td>
<td>20</td>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td>Vasoconstriction of excised rabbit auricle</td>
<td>20</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Contraction of excised toad sino-auricle</td>
<td>20</td>
<td>0.2</td>
<td>10</td>
</tr>
</tbody>
</table>

II. Peripheral effects of thiamine

As was anticipated from the experiments of the excised small intestine above mentioned, one of the sites of peripheral actions of thiamine appeared to be in the ganglion. Further studies were also made to clarify the site of action of thiamine and the antagonistic site of thiamine against nicotine in vivo.

a) Effects on blood pressure in dogs

A decrease of blood pressure was observed following administration of more than 5 mg/kg of thiamine, although the grade of the decrease varied individually.

The pressor effect of nicotine was obviously inhibited by the pretreatment of thiamine. On the other hand, the pressor effect of 1–2 μg/kg of epinephrine was not influenced following a pretreatment with 10 mg/kg of thiamine, but that of the occlusion of bilateral common carotid arteries was markedly inhibited (Fig. 2). The depressor effect of 1–2 μg/kg of acetylcholine was never inhibited, but was apparently accelerated following a pretreatment with 10 mg/kg of thiamine, but the depressor effect due to stimulation of the peripheral vagal nerve was markedly inhibited (Fig. 3).

b) Effects on the contraction of the nictitating membrane in cats

Contracting responses of the cat's nictitating membrane to a supramaximum stimulation of cervical sympathetic preganglionic fibers were moderately depressed follow-
ing a pretreatment with 20 mg/kg of thiamine and markedly depressed with 30 mg/kg of thiamine, though 10 mg/kg of thiamine showed no effects on responses. However, contracting responses induced by 5 μg/kg of epinephrine were not influenced by a pretreatment with 30 mg/kg of thiamine (Fig. 4). It has been demonstrated from the above results that thiamine had a ganglion blocking property, indicating a site of action located at the ganglion.

c) Effects on nicotine induced hyperglycaemia

Subcutaneous administration of 1 mg/kg of nicotine resulted in a 50 per cent increase of blood sugar over a normal level. The hyperglycaemic action due to nicotine was significantly inhibited by a pretreatment with 10 mg/kg of thiamine and completely inhibited with 20 mg/kg of thiamine (Table 3a). The hyperglycaemic action of nicotine

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**Fig. 2.** a) Effects of thiamine on the pressor action of epinephrine in dog.
Ad : Epinephrine 2 μg/kg
T : Thiamine 5 mg/kg
T2 : Thiamine 10 mg/kg

b) Influences of thiamine on the pressor effect by occlusion of bilateral common carotid arteries.
X : Occlusion of bilateral common carotid arteries (1 min)
T1 : Thiamine 10 mg/kg
T2 : Thiamine 1 mg/kg
T3 : Thiamine 5 mg/kg

**Fig. 3.** a) Influences of thiamine on the depressor effect of acetylcholine.
ACh : Acetylcholine 1 μg/kg
T1 : Thiamine 5 mg/kg
T2 : Thiamine 10 mg/kg

b) Influences of thiamine on the depressor effect due to stimulation of peripheral vagus.
○ : Stimulation of peripheral vagus (5 sec)
T : Thiamine 10 mg/kg
was inhibited by such drugs as phenobarbital, hexamethonium and dibenamine, but not by urethan (Table 3b). Reserpine, administered at a dosage of 1-2 mg/kg once daily for three consecutive days, inhibited the hyperglycaemic action of nicotine. Thiamine and hexamethonium employed at a dosage to inhibit the nicotine induced hyperglycaemic action resulted in a slight inhibition of the epinephrine-induced hyperglycaemia (Table 4).

From the above results, it is considered that the mechanism of the inhibition due to thiamine is not only attributable to a decreased release of epinephrine from the adrenal medulla, but also to a factor which has no relation to the decreased release of epinephrine.
III. Effects of thiamine on mortality and convulsions induced by nicotine

a) LD₅₀

LD₅₀ of nicotine was increased about 30 per cent with a statistical significance by 100 mg/kg of thiamine administered 30 minutes before the administration of nicotine (Table 5). Thiamine propyl disulfide (TPD) which forms a thiazole ring in vivo as reflected on the reports by Matsu kawa et al. (17) also increased LD₅₀ of nicotine to about 30 per cent with a pretreatment of 106 mg/kg either 30 minutes or 60 minutes before the administration of nicotine. LD₅₀ of nicotine changed with changes in the pretreatment interval of thiamine or TPD, which showed a reverse attitude to each other (Fig. 5).

b) Convulsions

1) Inhibitory effects of thiamine and TPD on convulsions induced by nicotine

The development of convulsions in albino rats pretreated with subcutaneous administration of 200 mg/kg of thiamine at 5, 10, 20 and 30 minutes before intramuscular...
injection of nicotine was observed. Thiamine obviously inhibited convulsions resulting in a decrease of the frequency and the duration of convulsions (Table 6). Also, the symptoms caused by injection of nicotine, such as, tremor, apnea, were markedly improved, but paralytic symptoms remained for a considerable time. Inhibition of the nicotine-induced convulsions with 212 mg/kg of TPD preadministered subcutaneously was plotted at intervals of 15, 30, 60 and 90 minutes (Fig. 6).

Thiamine and TPD took a reverse attitude of inhibition with an increase of pretreatment interval to each other. Two hundred milligrams per kilogram of vitamin B₁ was noneffective to convulsions.

2) Effects of thiamine on the convulsions due to electroshock and chemoshock

One hundred to 200 mg/kg of thiamine administered previously had no influences on the convulsions due to either electroshock or chemoshock by pentylentetrazol, strychnine and picrotoxin.

IV. Effects of thiamine on antidiuretic actions

No influences of 200 mg of thiamine administered intravenously on water diuresis were observed (Fig. 7). Following smoking, general symptoms such as pallor, nausea and occasional vomiting, extremital tremor, tachypnea and tachycardia, occurred and recovered 5-10 minutes after the discontinuance of smoking. The subsequent water diuresis was markedly

---

**TABLE 6. The influence of thiamine on nicotine-induced convulsion.**

<table>
<thead>
<tr>
<th>Pretreatment interval (min)</th>
<th>No. of animals</th>
<th>No. of animals convulsed</th>
<th>Recovery interval (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83</td>
<td>80</td>
<td>10-20</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>1</td>
<td>10-23</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>2</td>
<td>8.14</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>1</td>
<td>2-11</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>0</td>
<td>9-20</td>
</tr>
</tbody>
</table>

Nicotine 20 mg/kg
Thiamine 200 mg/kg

---

**FIG. 6. Inhibition of nicotine-induced convulsions in rats by thiamine and TPD.**

Nicotine 2 mg/kg

**FIG. 7. Effects of thiamine on water diuresis.**

--- Control
--- Thiamine 200 mg
depressed followed by a gradual recovery being represented by a two-peak curve (Fig. 8). Preadministration of 100-200 mg of thiamine reduced the period of antidiuretic action due to smoking (Table 7), but showed no influences on the antidiuretic action due to 100 mU of Atonin which was an extract of the posterior lobe of pituitary (Table 8, Fig. 9).

FIG. 8. Effects of thiamine on the antidiuretic action of smoking.
The numerals indicate the doses of thiamine.

TABLE 7. Influences of thiamine on the duration of the antidiuretic action due to smoking.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Inhibition time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
</tr>
<tr>
<td>3</td>
<td>105</td>
</tr>
<tr>
<td>4</td>
<td>180</td>
</tr>
<tr>
<td>5</td>
<td>105</td>
</tr>
</tbody>
</table>

mean 132.5 ± 30.7 85 ± 7.1 50 ± 7.1

Table 8. Effects of thiamine on the antidiuretic action of posterior pituitary extract.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Inhibition time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
</tr>
</tbody>
</table>

FIG. 9. Effects of thiamine on the antidiuretic action of posterior pituitary extract.

----- Control
---- Thiamine 200 mg

V. Effects of thiamine related compounds on nicotine-induced contraction of the excised small intestine

The relative potency of thiamine related compounds on the inhibition of the contraction induced by 5 mg/20 ml of nicotine was summarized in Table 9. The molar concentration of each compound, which was equivalent to the potency of 5 mg/20 ml of thiamine was expressed in the parenthesized figures and the degree of antinicot ine action in the same concentration was shown as follows:

Complete antagonism*; moderate antagonism +; no antagonism –.

Among these compounds tested, phenylthiazole derivatives, for example, 2,4-diamino-5-phenylthiazole, 2-amino-4-phenylthiazole, showed a complete antagonizing action against the action of nicotine in less concentration than the equi-


THIAMINE AS NICOTINE ANTAGONIST

TABLE 9. Relative potency of the anti-nicotine action of thiamine related compounds on the rabbit and the guinea pig intestines.

<table>
<thead>
<tr>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>Water solubility</th>
<th>Anti-nicotine potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₄</td>
<td>C₂H₅OH</td>
<td>Sparingly soluble</td>
<td>+ (1)</td>
</tr>
<tr>
<td>NH₂·HCl</td>
<td>CH₄</td>
<td>C₂H₅OH</td>
<td>+ (1)</td>
<td></td>
</tr>
<tr>
<td>NH₂</td>
<td>H</td>
<td>H</td>
<td>Sparingly soluble</td>
<td>+ (1)</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>CONNH₂</td>
<td>(Freely soluble in NaOH)</td>
<td>- (2)</td>
</tr>
<tr>
<td>SH</td>
<td>CH₃</td>
<td>CONNH₂</td>
<td></td>
<td>- (2)</td>
</tr>
<tr>
<td>NH₂</td>
<td>H</td>
<td>C₂H₅SO₄NH₂·HCl</td>
<td></td>
<td>+ (1)</td>
</tr>
<tr>
<td>NH₂·HBr</td>
<td>NH₂</td>
<td>C₄H₅</td>
<td>++ (1/4)</td>
<td></td>
</tr>
<tr>
<td>NH₂·HBr</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>++ (1/16)</td>
<td></td>
</tr>
<tr>
<td>NH₂</td>
<td>CH₃</td>
<td>H</td>
<td>++ (1/8)</td>
<td></td>
</tr>
</tbody>
</table>

The parenthesized value represents the molar concentration ratio being equivalent to the same activity of thiamine.

TABLE 10. Anti-nicotine action of water soluble vitamins (by Magnus' method).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Pretreated doses (mg/20 ml)</th>
<th>Anti-nicotine activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Pyridoxal</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

The antinicotine action of other water soluble vitamins was not demonstrated (Table 10).

DISCUSSION

Clark has already classified the drug antagonism into three forms: chemical, physiological and specific (18). Because of the lack of a definite conclusion from the author's department (8, 9) or Pick's previous works (13, 19–21), in establishing that the antagonism between nicotine and thiamine is not of chemical origin, the present experimentation was performed to confirm whether the antagonism is chemical, using a previously mixed solution containing various doses of nicotine and thiamine in several kinds of excised organs. As indicated in the results in which the ratio of a thiamine dose sufficient to antagonize a nicotine dose was extremely different depending upon the organ employed, it is concluded that the antinicotine action of thiamine is not valent concentration of thiamine.

Clark has already classified the drug antagonism into three forms: chemical, physiological and specific (18).
merely referable to a simple chemical antagonism, but a biological one which is related to a drug receptor. On the basis of the study of PA, values of several pharmacologically related compounds for nicotine and the study of variations of nicotine concentration activity curve by thiamine, it is strongly supported to assume that the antinicotinic action of thiamine is involved in the competition in the receptor site.

The finding that thiamine predominatingly antagonizes nicotine rather than acetylcholine and histamine in the excised guinea pig's small intestine will suggest that one of the main acting sites of thiamine seems to be in the ganglion.

In the experiment on blood pressure in dogs thiamine clearly showed a depressor action at a single dose. Thiamine showed no influences on the pressor action due to epinephrine, but the pressor effect due to the electric stimuli of the peripheral vagal nerve was found responsive to thiamine. In the present study concerning the nictitating membrane of cats, thiamine definitely inhibited the contraction induced by electric stimuli of presynaptic fibers of the cervical sympathetic nerve, in accordance with the report by Mazzella et al. (22), but showed no marked effect on the contraction due to epinephrine.

From these results, it is concluded that thiamine has a decisive ganglion blocking action and that a main antagonistic site in the peripheral region is the nervous ganglion.

Although Haley et al. (23, 24) already demonstrated referring to Pick's results that the depressor action induced by thiamine administered intravenously in rabbits was probably due to a paralysis of the postganglionic fiber ending on the blood vessel wall itself. It seems safe to emphasize that the mechanism of this depressor action by thiamine was mainly attributable to the ganglion blocking action. That shock like symptom evoked by thiamine with a dose usually employed is sometimes observed in clinic may prove an importance of the ganglion blocking action of thiamine.

It has been observed that thiamine inhibits only convulsions induced by nicotine, but not by strychnine, picrotoxin, pentylenetetrazol and electroshock. Also LD₅₀ of nicotine due to thiamine was found to increase, although such increase by thiamine was not so intensive as pointed out by one of the present author's colleagues (11).

Laurence et al. (25) reported that a selective inhibition of nicotine convulsions by hexamethonium and pentamethonium in mice and rats was not due to an antagonism in the central nervous system, but due to an inhibition of epinephrine release which was induced by nicotine from the adrenal medulla. Referring to the present experimental results with nicotine induced hyperglycaemia, it dose not seem that the antagonism between nicotine and thiamine is solely attributable to the inhibition of a release of epinephrine. In order to further pursue the antinicotinic action of thiamine in the central nervous system, studies were made of the effects of thiamine on the anti-diuretic action which is regarded as one of the central action of nicotine. At a dose which has no influences on water diuresis, thiamine significantly antagonized the anti-diuretic action due to smoking, but not what was due to Atonin. Consequently it is
assumed that thiamine has also an antagonistic action on nicotine in the hypothalamo-posterior pituitary system.

Supek et al. (26) have already suggested that the hypothalamo-posterior pituitary system as a nicotine receptor takes a different attitude from that in the other sites because of the fact that pentamethonium, tetraethylammonium, Diparcol and procaine have no influence upon the antidiuretic action of nicotine and that only phenobarbital in the anesthetic dose remarkably antagonizes it. The results seem to indicate that thiamine is essentially a specific nicotine antagonist with properties different from those of the so-called nicotinolytic drugs.

Among the thiamine derivatives employed in the present study the antinocotine action was demonstrated in the following compounds: 2-amino-4-methyl-5-hydroxyethyl-thiazole, 2-amino-4-phenylthiazole and 2-amino-4-methyl-5-phenylthiazole in thiazole group and 2-methyl-4-aminopyrimidinyl-(5)-carbohydrazide in pyrimidine group. Some of the phenylthiazole compounds are possessed with less molar concentration than thiamine. Thiadiazole compounds, regardless of the presence of amino radical in 2 position, did not show any antinocotine action at all. Information on these experimental results suggested that in thiazole derivatives the amino radical in 2 position was essential and the presence of phenyl radical accelerated antinocotine activities.

The antagonism between nicotine and thiamine dealt with in this paper, being also discussed in the author's other report (11), is by no means referrable to the action of thiamine as a vitamin.

However, the recent development of vitamin treatment with a large dose, may be useful in abbreviating various harmful conditions induced by smoking, considering a pharmacological antagonism between nicotine and thiamine.

**SUMMARY**

In a serial study on nicotine metabolism and its detoxication, thiamine proved to be antagonistic to nicotine in various organs in vitro and this antagonism was stronger than one of acetylcholine or histamine suggesting that one of the principal sites of action of thiamine is located in the nervous ganglion. From activity-concentration curves, this antagonism appeared to be a so-called competitive one being more typical than those of hexamethonium and TEA. Thiamine has a vasodepressing action in dogs, being associated with no adrenergic action, but it is antagonistic to the pressor effect induced by nicotine or by bilateral occlusion of the common carotid arteries. Thiamine inhibits depressor responses to presynaptic vagal stimulation due to electric stimuli. These findings and those obtained from experiments on the cat’s nictitating membrane may illustrate a ganglion blocking effect of thiamine. It is assumed that thiamine improves hyperglycaemia which is represented by the release of epinephrine which was caused in rabbits following administration of nicotine.

Antidiuresis by cigarette smoking was significantly inhibited by thiamine in man while it exerted no influence on the antidiuresis induced by a pituitary posterior
lobe extract, suggesting that a nicotine antagonism by thiamine is connected with the hypothalamo-posterior pituitary system.

Among the related compounds of thiamine, thiazole derivatives containing an amino group at "2" and/or phenyl group at other than "2" elicited an augmentation in antagonistic activity to nicotine.

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