THE SYMPATHOMIMETIC EFFECTS OF SKF-385 ON BLOOD PRESSURE IN DOG

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The chemical structure of SKF-385, the potent monoamine oxidase inhibitor, is closely related to that of methamphetamine. The sympathomimetic effects of SKF-385 have already been reported (1, 2). Shideman et al. (1) and Horita et al. (3) have concluded that the sympathomimetic effects of SKF-385 as well as phenyl-isopropyl hydrazine (Catron) derived from the release of endogenous noradrenaline rather than from the inhibitory effect of the drugs on the monoamine oxidase. The adrenaline-like stimulating effects of SKF-385 on the isolated auricular preparation of rabbit (Toda, unpublished) and on the transmembrane potentials of the isolated atrium of rabbit (4) have been confirmed in this laboratory. Toda and Tachi also showed that the administration of SKF-385 retarded the manifestation of the depressive effects of reserpine on the rhythmical contraction and the action potential of the isolated atrium. They further showed that although the isolated atrium depressed by addition of reserpine was not recovered by the washing-out of reserpine from the preparation, the isolated atrium of rabbit which had previously received SKF-385 was also depressed by addition of reserpine in vitro, but was easily recovered by the washing-out of reserpine from the preparation. Matsuo (5) in this laboratory showed that the administration of SKF-385 to the isolated atrium increased the content of noradrenaline in the tissue, and that the administration of reserpine to the isolated atrium pretreated with SKF-385 markedly increased the content of noradrenaline. From these results, the suggestion that the effect of SKF-385 on the atrium might correlate with the release of noradrenaline seems to be doubtful.

On the other hand, Burn and Rand (6) have proposed the working hypothesis that the sympathomimetic effects of amphetamine derived from the release of the endogenous noradrenaline, and that the tachyphylaxis caused by the repeated injection of the drug derived from the consumption of the stored amine. The sympathomimetic effects of SKF-385 on the blood pressure easily subjected to tachyphylaxis by the repeated injection.

The mode and mechanism of the sympathomimetic effect of SKF-385 have been analyzed in the anesthetized dog, whose blood pressure had shown a marked tachyphylaxis against the drug.

METHODS

Mongrel dogs, weighing 5 to 10 kg, were used in this experiment. The animal was anesthetized with the intraperitoneal injection of 80 to 120 mg/kg of amobarbital sodium.
The blood pressure measured from cannulated common carotid artery was recorded on the smoked paper via a mercury manometer. In some experiments the spinal dog, of which the spinal cord was transected between C2 and C5 under ether anesthesia, was used under the artificial respiration. For the reserpinization of the animal, 0.5 mg/kg of the drug was injected intraperitoneally 16 to 20 hours before the operation.

All drugs were injected via a femoral vein. The following drugs were employed: trans dl-2-phenylcyclopropyl amine maleate (SKF-385, Parnate), methamphetamine hydrochloride, l-adrenaline hydrochloride, dl-noradrenaline hydrochloride, tyramine hydrochloride, reserpine, 2-benzyl-4,5-imidazoline hydrochloride (tolazoline), dibenamine hydrochloride, diphenhydramine hydrochloride (Benadryl), atropine sulfate and dichloroisoproterenol hydrochloride (DCI).

RESULTS

1) Effects of SKF-385 on the blood pressure

The intravenous injection of 0.1 to 3.0 mg/kg of SKF-385 elevated the blood pressure. The extent and duration of the rise of blood pressure by the drug depended on the dose administered. When the administration of SKF-385 was repeated again and again, the depressor response of the animal to SKF-385 was usually obtained. Thereafter, the extent of the fall of blood pressure by SKF-385 was depended on the dose administered.

The rise of blood pressure in response to the first dose of 0.5 mg/kg of SKF-385 was slight and transient. When the same dose of SKF-385 was repeated after the termination of the pressor response to the preceding administration, the pressor response increased until the total dose became to 2.0 to 3.0 mg/kg. Thereafter, the pressor response to the dose of 0.5 mg/kg of SKF-385 began to decrease and at last the depressor response was observed (Fig. 1 and Table 1).

The intravenous injection of 1.0 mg/kg of SKF-385 also elevated the blood pressure. The extent and duration of the rise of blood pressure by the dose of SKF-385 were much larger and longer than those of blood pressure induced by 0.5 mg/kg of the drug. The repeated injection of the same dose of SKF-385 revealed less pressor effect and
after the total dose of SKF-385 summed up 3.0 to 4.0 mg/kg, the depressor response to 1.0 mg/kg of SKF-385 was observed (Table 1).

The rise of blood pressure in response to the intravenous injection of 2.0 mg/kg of SKF-385 varied from dog to dog, ranging from 28 to 116 mmHg. The blood pressure after the total dose of SKF-385 summed up 3.0 to 4.0 mg/kg, the depressor response to 1.0 mg/kg of SKF-385 was observed (Table 1).

The rise of blood pressure in response to the intravenous injection of 2.0 mg/kg of SKF-385 varied from dog to dog, ranging from 28 to 116 mmHg. The blood pressure peak.
rose steeply and reached its peak effect at 2 to 3 minutes after the injection. Thereafter, the elevated blood pressure fell initially fast and later very slowly as shown in Fig. 2, and recovered to the level of blood pressure before the injection at one to one and half hours. The second injection of the same dose of SKF-385 usually revealed a fall of blood pressure followed by a small rise. Further injection of the same dose of SKF-385 abolished the pressor effect and the depressor response caused by further injection of SKF-385 remained constant (Fig. 2 and Table 1). The similar depressor effect caused by the repeated injection of SKF-385 was also observed in the spinal dog. The rise of blood pressure by 2.0 mg/kg of SKF-385 in the spinal dog was not so sharp as was observed in the anesthetized dog (Fig. 3).

When the depressor response of the animal to 2.0 mg/kg of SKF-385 was attained by the repeated injection, the administration of 2.0 mg/kg of methamphetamine revealed almost the same extent of the fall of blood pressure as the administration of the same dose of SKF-385. The repeated administration of 2.0 mg/kg of methamphetamine also induced a depressor response of the animal to the same dose of SKF-385. In this case also, the administration of 2.0 mg/kg of SKF-385 induced a fall of blood pressure approximately as large as the administration of the same dose of methamphetamine (Fig. 4). These results show the cross-tachyphylaxis between SKF-385 and methamphetamine.

![Fig. 2. Cross tachyphylaxis between methamphetamine and SKF-385.](image)

The third injection of 2.0 mg/kg of methamphetamine induced only a depressor response and 60 minutes later the same dose of SKF-385 induced the similar response.

2) Effects of SKF-385 on the pressor effect of adrenaline and noradrenaline

The administration of 0.5 mg/kg of SKF-385 potentiated the pressor effect of 1.0 to 5.0 µg/kg of adrenaline. But after the second dose of SKF-385 the injection of 1.0 to 5.0 µg/kg of adrenaline revealed an increased rise of blood pressure followed by a slight fall. Thereafter, further administration of 0.5 mg/kg of SKF-385 decreased the rise and increased the fall of blood pressure in response to 1.0 to 5.0 µg/kg of adrenaline.

The administration of 2.0 mg/kg of SKF-385 decreased the pressor response to 1.0 to 5.0 µg/kg of adrenaline and induced a fall of blood pressure from the end of the pressor response. The second injection of 2.0 mg/kg of SKF-385 more reduced the pressor effect and increased the depressor effect in extent and in duration. Further repeated injection of SKF-385 markedly diminished the pressor effect induced by adrenaline and the depressor
The depressor effect of 5.0 μg/kg of adrenaline on the animal which had repeatedly received SKF-385 in total dose of 6.0 mg/kg for about 5 hours and shown a depressor response to 2.0 mg/kg of SKF-385, was reversed by the intravenous injection of 10 mg/kg of DCI. A marked pressor response to 5.0 μg/kg of adrenaline after the injection of DCI, illustrated in Fig. 6, is contrast to the biphasic effect of the same dose of the amine (Fig. 5-III) in the animal injected SKF-385 repeatedly. However, the depressor effect induced by the injection of 2.0 mg/kg of SKF-385 was not significantly affected by DCI (Fig. 6).
The pressor effect of noradrenaline was similarly affected by SKF-385 and DCI as that of adrenaline. The depressor effect of 1.0 to 5.0 µg/kg of noradrenaline on the blood pressure of animal injected SKF-385 repeatedly, was usually much less than the response elicited by the same dose of adrenaline.

3) Effects of atropine and benadryl on the depressor effect of SKF-385

The administration of 0.5 to 2.0 mg/kg of atropine or 1.0 to 3.0 mg/kg of benadryl did not affect the depressor effect of SKF-385 in the animal which had been treated with the repeated injection of 2.0 mg/kg of SKF-385 (Fig. 6). From the results the cholinergic or histaminergic depressor effect of SKF-385 could be excluded. As was described above, DCI did not block the depressor effect of SKF-385. It was likely that the depressor effect of SKF-385 was independent from the depressor mechanism of catecholamines which was blocked by DCI.

4) Effects of tolazoline and dibenamine on the depressor effect of SKF-385

The intravenous injection of 10 mg/kg of tolazoline in the anesthetized dog often induced a slight elevation of blood pressure. But the same procedure of tolazoline to the animal which had received repeated dose of SKF-385 and shown a depressor response to the injection of 2.0 µg/kg of SKF-385, always caused a considerable and prolonged fall of blood pressure (Fig. 6). After the injection of tolazoline the depressor effect of 2.0 mg/kg of SKF-385 disappeared and some rise of blood pressure was observed (Fig. 6). Even in the normal dog, the pretreatment of the animal with 10 mg/kg of tolazoline or 15 mg/kg of dibenamine reversed the pressor effect of adrenaline and depressed the pressor effect of 2.0 mg/kg of SKF-385. In the animal pretreated with the above-described dose of tolazoline or dibenamine the repeated injection of 2.0 mg/kg of SKF-385 never induced a fall of blood pressure, though the depression of the pressor effect by SKF-385 was observed along with repetition of the injection (Fig. 7 and Table 2).

![Fig. 7. Effect of dibenamine (15 mg/kg) on the pressor and depressor responses of SKF 385 (2.0 mg/kg). I: responses to adrenaline (5.0 µg/kg), dibenamine (15 mg/kg), adrenaline (5.0 µg/kg) and first SKF-385 (2.0 mg/kg). II: the third injection of SKF-385. III: the fourth injection of SKF-385.](image-url)
From the results described above, it was likely to conclude that tolazoline as well as dibenamine not only depressed the pressor effect but also blocked the depressor effect caused by the injection of SKF-385. The gradual decrease of the pressor response of the animal to the repeated dose of SKF-385 might have derived from the tachyphylaxis of the drug.

5) Effects of SKF-385 on the blood pressure of dog pretreated with reserpine

The rise of blood pressure of the animal, pretreated with 0.5 mg/kg of reserpine 16 to 20 hours before, in response to 200 μg/kg of tyramine was in the range from 12 to 16 mmHg, while the rise of blood pressure of the normal dog was in the range from 62 to 90 mmHg (Fig. 8-I and II). The first injection of 2.0 mg/kg of SKF-385 to the reserpinized animal revealed a usual pattern of pressor effect, in which the rise of blood pressure ranged from 28 to 76 mmHg and returned to the normal level one hour or more later. This effect of SKF-385 on the blood pressure of reserpinized dog was similar

<table>
<thead>
<tr>
<th>Drug-pretreatment</th>
<th>Dose (mg/kg)</th>
<th>Initial blood pressure level (mmHg)</th>
<th>Blood pressure response (mmHg) to injection of SKF-385 (2.0 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1st inj. 2nd 3rd 4th 5th 6th 7th</td>
</tr>
<tr>
<td>Tolazoline</td>
<td>10</td>
<td>90</td>
<td>10 – 4 4 4 4 8 8</td>
</tr>
<tr>
<td>Tolazoline</td>
<td>10</td>
<td>80</td>
<td>22 4 4 4 4 8 8</td>
</tr>
<tr>
<td>Tolazoline</td>
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<td>130</td>
<td>24 6 4 5 5</td>
</tr>
<tr>
<td>Dibenamine</td>
<td>10</td>
<td>80</td>
<td>20 2 2</td>
</tr>
<tr>
<td>Dibenamine</td>
<td>15</td>
<td>90</td>
<td>54 2 2</td>
</tr>
</tbody>
</table>

*: response to methamphetamine (2.0 mg/kg)

Fig. 8. Effect of SKF-385 on the blood pressure of reserpinized dog.
I: response to tyramine (200 μg/kg) on the blood pressure of untreated dog
II: response to the same dose of tyramine on the blood pressure of reserpinized dog
III–VI: effects of the first, third and fourth injection of SKF-385 on the blood pressure of reserpinized dog.
in extent and duration to that on the blood pressure of normal dog, while the pressor
effect of tyramine on the former blood pressure was apparently less than that on the
latter. Further the pressor response to the repeated injection of the same dose of SKF-385
decreased progressively. However, any depressor response to the dose of SKF-385 could
not be observed even if the injection of SKF-385 was repeated many times (Fig. 8-III,
IV, V and Table 3).

From the results described above, it was likely to suggest that the manifestation of the
pressor effect of SKF-385 scarcely correlated with the normal content of catecholamines
in the organs and tissues, and that the depressor effect of SKF-385 was demonstrated only
when the content of catecholamines in the tissues was normal and when the pressor
response was fully blocked by the SKF-385 tachyphylaxis.

6) Effects of reserpine on the blood pressure of the animal pretreated with the repeated administration of SKF-385

The pretreatment of the dog with 0.5 mg/kg of SKF-385 reversed the reserpine effect
on the blood pressure of anesthetized dog, in which only the pressor response was
observed. The animal, which had received the repeated dose of 2.0 mg/kg of SKF-385
and revealed only a depressor effect by the administration of 2.0 mg/kg of SKF-385,
showed a considerable and long-lasting fall of blood pressure preceded by a slight and
transient rise in response to the intravenous injection of 0.5 mg/kg of reserpine (Fig. 9).
The duration of the depressor effect was approximately as long as that of the pressor

<table>
<thead>
<tr>
<th>Exper. No.</th>
<th>Initial blood pressure level (mmHg)</th>
<th>Blood pressure response (mmHg) to SKF-385 (2.0 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st inj. 2nd 3rd 4th</td>
</tr>
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<td>1</td>
<td>90</td>
<td>76 24 -- 8</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>66 44 34 20</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>42 44 8 16</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>32 20 18 14</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>28 20 20</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>22 8 8</td>
</tr>
</tbody>
</table>

Fig. 9. Effect of reserpine (0.5 mg/kg) after the manifestation of depressor response to SKF 385 (2.0 mg/kg) on the blood pressure.
effect caused by the injection of the same dose of reserpine in the animal pretreated with a single dose of 0.5 mg/kg of SKF-385. This depressor effect of reserpine was also blocked by the injection of 10 mg/kg of tolazoline or 15 mg/kg of dibenamine.

From the results obtained it was concluded that the pretreatment of the animal with a small dose of SKF-385 reversed the action of reserpine, while the pretreatment of the animal with large dose of SKF-385 blocked the pressor effect of reserpine and induced a long-lasting fall of blood pressure. The former effect seemed probably to coincide with the potentiating effect of small dose of SKF-385 on the pressor effect of catecholamines liberated by reserpine, and the latter effect seemed to derive from the reversing effect of large dose of SKF-385 on the pressor action of the amines liberated by reserpine.

![Figure 10](image.png)

**Figure 10.** Potentiating effect of SKF-385 on the pressor response to tyramine (50 μg/kg). Tyramine was injected 80 minutes after 0.5 mg/kg of SKF-385 and was injected 60 minutes thereafter.

**Table 4.** Responses to tyramine (30 μg/kg) before and after SKF-385 in a dose of 0.5 or 2.0 mg/kg.

<table>
<thead>
<tr>
<th>Initial blood pressure level (mmHg)</th>
<th>Blood pressure response (mmHg) to tyramine (30 μg/kg)</th>
<th>Hours after SKF-385 (0.5 mg/kg)</th>
<th>Hours after SKF-385 (2.0 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before SKF-385</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>90</td>
<td>18, 18</td>
<td>64.2.6</td>
<td>70.2.9</td>
</tr>
<tr>
<td>120</td>
<td>10, 10</td>
<td>42.3.2</td>
<td>45.3.5</td>
</tr>
<tr>
<td>130</td>
<td>30, 26</td>
<td>70.1.5</td>
<td>54.0.9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>100</td>
<td>16, 16</td>
<td>32.1.0</td>
<td>26.0.6</td>
</tr>
<tr>
<td>80</td>
<td>20, 18</td>
<td>30.0.6</td>
<td>18.0.0</td>
</tr>
</tbody>
</table>

*: 22 mmHg of rise followed by a fall (2 mmHg) of blood pressure.  
**: rise followed by a fall (4 mmHg) of blood pressure. Figures in parentheses represent the increasing ratios which were calculated from a − b, where a is response to tyramine after SKF-385, b is the response before SKF-385.
7) Effects of tyramine on the blood pressure of the animal pretreated with SKF-385

The pressor effect of 50 μg/kg of tyramine was markedly increased in magnitude and in duration by the previous injection of 0.5 mg/kg of SKF-385 (Fig. 10 and Table 4). Though the previous administration of 2.0 mg/kg of SKF-385 increased the pressor effect of 50 μg/kg of tyramine, the increase of the rise of blood pressure caused by 2.0 mg/kg of SKF-385 was not so marked as that caused by 0.5 mg/kg of the drug (Table 4). The rise of blood pressure in response to 50 μg/kg of tyramine was most marked at one hour after the administration of 2.0 mg/kg of SKF-385 and thereafter the pressor effect of tyramine tended to reduce. The administration of 200 μg/kg of tyramine to the animal, which had received repeated dose of SKF-385 and shown a depressor response to the injection of 2.0 mg/kg of SKF-385, induced a slight fall of blood pressure preceded by moderate rise.

The results showed that the injection of SKF-385 in the dose used in this experiment increased the pressor effect of 50 μg/kg of tyramine. The effect of SKF-385 on the pressor action of tyramine contrasted with the biphasic effect of SKF-385 on the pressor action of adrenaline.

DISCUSSION

The mode of the sympathomimetic effect of SKF-385 was studied in dog by use of the response of blood pressure. There may be some criticism that the responses to the sympathomimetic amines derived from too complicated mechanism to draw a clear-cut conclusion from the results obtained by the blood pressure. Therefore, this experiment was designed to obtain a correlation between the effects of SKF-385 on the transmembrane potential of the rabbit's heart (4) or on the content of norepinephrine in the rabbit's heart (5) and the effects of the drug on the blood pressure.

The intravenous injection of SKF-385 induced a rise of blood pressure. The rise of blood pressure in response to the small dose of the drug (0.5 mg/kg) was slight and transient, and the repetition of the administration of the small dose increased the rise of blood pressure until the total dose of the drug given amounted to 3.0 to 4.0 mg/kg. Thereafter, further repetition of the injection of the same dose decreased the rise of blood pressure and at last the injection of 0.5 mg/kg induced a biphasic effect, the rise of blood pressure preceded by a transient fall. The intravenous injection of large dose (2.0 mg/kg) of SKF-385 induced a rise of blood pressure which lasted for one to one and half hours. Usually, the second injection of large dose of the drug induced a biphasic effect or only a fall of blood pressure. The further injection of the same dose of SKF-385 induced a fall of blood pressure which was not increased by the repetition of the injection. The fall of blood pressure was sharp but short lasting. The similar reversal of pressor effect of methamphetamine was also observed in the dog (7). The mutual reversal of the pressor effect between methamphetamine and SKF-385 was confirmed in this experiment. From the results it is concluded that SKF-385 shows pressor and depressor effects on the blood pressure in the anesthetized dog, and that the depressor effect of the drug manifests
only when the pressor receptor is saturated with SKF-385 itself or methamphetamine and the pressor effect has been disappeared. Assuming that methamphetamine releases and depletes noradrenaline in the central nervous system (8), heart and adrenal gland and that SKF-385 releases but cumulates noradrenaline in various tissues including heart (5), the similarity of the pressor and depressor effects between methamphetamine and SKF-385 is a paradoxical phenomenon.

The injection of the small dose of SKF-385 as well as methamphetamine potentiated the pressor effect of adrenaline. This potentiating effect of SKF-385 may correlate with the inhibition of monoamine oxidase by the small dose of the drug. However, the potentiating effect of SKF-385 did not increase along with the increase of the dose, and on the contrary large dose of SKF-385 reversed the pressor effect of adrenaline. The reversal of the pressor effect of adrenaline by large dose of SKF-385 or by the repeated injection of the small or moderate dose of SKF-385 indicates that the administration of large dose of SKF-385 or the saturation of the body with the drug blocks the pressor receptor. This result also allows the conclusion that the depressor effect of adrenaline or SKF-385 manifests only when the pressor receptor is blocked by large dose of SKF-385. Further conclusion that the administration of large dose of SKF-385 does not block the depressor receptor could be drawn. Burn and Rand (6) postulated that the pressor effect of methamphetamine derived not from the direct effect of the drug on the receptor, but from the effect of noradrenaline released from the stored sites by methamphetamine. They further suggested that the tachyphylaxis of methamphetamine related with the consumption of stored noradrenaline by the large dose of the drug. If their assumption would be, the depressor effect of methamphetamine seems not to relate with the endogenous noradrenaline and therefore seems to derive from the direct action of the drug on the depressor receptor. Burack et al. (9) have shown that noradrenaline in the cytoplasm binds with protein-adenine nucleotide. It has been suggested by Schümann and Philippu (10) that the administered tyramine replaced with a part of endogenous catecholamines in the adrenal medullary granules and, as a result, the amines were liberated from their bound sites. The replacement of methamphetamine with the endogenous noradrenaline in the tissue is considered from the results shown by Young and Gordon (11) that adrenaline or noradrenaline affected the uptake of amphetamine-14C by rat-brain. If the administered methamphetamine takes over the sites of its binding and releases the bound noradrenaline, it may be reasonable to consider that SKF-385, of which chemical structure is closely related to methamphetamine, behaves similarly. The biochemical assay of noradrenaline, as described above, is against the release of endogenous noradrenaline by SKF-385. However, no evidence is presented yet to show that the accumulated noradrenaline in the tissue is a bound form and not a free form.

The administration of 10 mg/kg of DCI, which blocked the depressor effect and manifested a pressor effect of adrenaline in the dog pretreated with repeated injection of SKF-385, did not block the fall of blood pressure in response to 2.0 mg/kg of SKF-385. The results may show the difference of affinity of the depressor receptor between
adrenaline and SKF-385 in the presence of DCI.

After tachyphylaxis has developed by the repeated injection of SKF-385 the injection of tolazoline always induced a fall of blood pressure, while it usually induced a rise of blood pressure in the normal dog. The rise of blood pressure caused by tolazoline has been explained due to the cardiostimulant effect. The reversed effect of tolazoline in the animal pretreated with the repeated dose of SKF-385 is considered to derive from the saturation of the cardiostimulating receptor and from the remaining affinity of the cardioinhibitory receptor to SKF-385 (Toda, unpublished) after the repeated injection of large dose of the drug. Such an abolishment of the cardiostimulant effect of SKF-385 might have decreased the pressor response to SKF-385 and, consequently, might have increased the depressor response for which the vascular effect of the drug was mainly responsible.

The administration of the adrenolytic dose of tolazoline or dibenamine blocked the depressor effect of SKF-385 and induced a very slight sign of rise of blood pressure in the animal pretreated with the repeated injection of SKF-385. This result shows that tolazoline or dibenamine blocks the depressor effect of SKF-385, probably derived from the blockade of the binding of the depressor receptor with SKF-385 itself or with noradrenaline released by SKF-385. This may be a paradoxical phenomenon, considering from the adrenolytic property of tolazoline and dibenamine.

Though the pressor effect of tyramine was markedly depressed by the reserpinization of the animal, the same effect of the first injection of SKF-385 was not significantly modified. If the conclusion that the pressor effect of tyramine derives from the indirect action or the released norepinephrine by the drug would be (6, 12-14), the pressor effect of SKF-385 might not only relate with the liberation of norepinephrine but also in most part should be due to the direct effect on the pressor receptor. But the repeated injection of 2.0 mg/kg of SKF-385 to the reserpinized animal did decrease the pressor effect but never induced a depressor effect. Shideman et al. (1) reported that the cardiostimulant effect of several monoamine oxidase inhibitors, including SKF-385, were derived from released norepinephrine on the cat's papillary muscle and atrial preparation. In the present experiment it is considered that the depressor response to repeated SKF-385 which was blocked by reserpine-pretreatment, tolazoline or dibenamine, might correlate with norepinephrine released. Furthermore, the depressor mechanism of SKF-385 may be considered otherwise. Young and Gordon (11) have suggested the possibility that the degree of action of amphetamine might be regulated by circulating catecholamines. This may also explain the difference between the effects of SKF-385 on the blood pressure of dog with and without the pretreatment of reserpine. Schümann (15) suggested that reserpinization destroyed the protein-adenine nucleotide or protein-ATP complex within the cell which served to bind norepinephrine. If this assumption is allowed, the deterioration of the binding mechanism of the cell with norepinephrine induces the disappearance of the depressor response of SKF-385 in the animal which was treated with repeated injection of SKF-385. In other words, the pressor effect of SKF-385 manifests independently on
the content of noradrenaline in the reactive tissues and the manifestation of the depressor effect of the same drug requires the intact binding mechanism with noradrenaline.

The previous injection of the small dose of SKF-385 induced a pressor response to the injected reserpine, while the previous injection of the large dose of SKF-385 induced a fall of blood pressure preceded by a slight rise. The former effect is supposed to derive from the potentiating effect of SKF-385 on the pressor action of noradrenaline released by reserpine, and the latter effect of SKF-385 is supposed to be due to the depression or blockade of the pressor response to noradrenaline released by reserpine.

The pressor effect to tyramine was augmented by SKF-385 in a single dose of 0.5 to 2.0 mg/kg, especially 0.5 mg/kg. This effect may be accounted from the complete inhibition of monoamine oxidase activity by SKF-385 as reported elsewhere (16, 17) and from the increase of noradrenaline content in the tissue after SKF-385 (5, 16). The result that the potentiating effect of a large dose of SKF-385 on the rise of blood pressure induced by tyramine was less than that of a small dose, supposedly correlates with the manifestation of the depressor response to a large dose of SKF-385. From this supposition it was difficult to understand the result that the pressor response to tyramine was hardly reversed by the repeated injection of a large dose of SKF-385. To obtain a clear-cut understanding of tyramine action more pharmacological or biochemical studies should be required.

From the discussions described above, the modes of action of SKF-385 are summarized as follows: 1) the direct pressor effect which reveals even in the absence of the endogenous noradrenaline and easily subjects to tachyphylaxis, 2) the direct or indirect depressor effect which is abolished by the depletion of endogenous noradrenaline caused by reserpine and is readily blocked by the adrenolytics such as tolazoline or dibenamine, 3) the potentiating effect of the small dose of the drug on the pressor effect of adrenaline or noradrenaline and of the large dose on the depressive effect, both of which may relate with the modes of action of the drug described above, and 4) the accumulation of noradrenaline in the tissues induced by the inactivation of the monoamine oxidase.

SUMMARY

The sympathomimetic effects of SKF-385 were studied by use of the blood pressure response of anesthetized dog. The result obtained are summarized as follows:

1. The first intravenous injection of SKF-385 evoked a pressor effect, in which the rise and the duration were usually proportional to the dose. The repeated injection of SKF-385 progressively decreased the pressor effect and manifested a biphasic effect, the slight rise of blood pressure preceded by a fall. When the total amounts of SKF-385 reached to 3.0 to 4.0 mg/kg by the repeated administration, the animal showed only a depressor effect to SKF-385. The depressor effect of a definite dose of SKF-385 was not further affected by the repetition of the drug administration.

2. The first pressor effect of 0.5 to 2.0 mg/kg of SKF-385 was not significantly affected by the reserpinization of the animal. The reserpinization of the animal did not affect
the progressive decrease of the pressor effect elicited by the repeated injection of the
dose of SKF-385, but the reserpinization blocked the depressor effect of SKF-385 which
was observed in the normal animal received SKF-385 repeatedly.

3. The administration of the adrenolytic dose of tolazoline or dibenamine depressed
the pressor effect of SKF-385, and moreover reversed or blocked the depressor effect of
SKF-385.

4. The administration of the small dose (0.5 mg/kg) of SKF-385 potentiated the
pressor responses of the animal to adrenaline, noradrenaline and tyramine. But when
the depressor response of SKF-385 had been demonstrated by the repeated injection of
the drug, the injection of adrenaline or noradrenaline induced a fall of blood pressure
or a small rise followed by a prolonged fall. On the other hand the pressor effect of
tyramine was difficult to reverse.

5. Only when the animal showed a depressor response to SKF-385 induced by the
repeated injection, the injection of reserpine evoked a transient and slight rise of blood
pressure followed by a marked and prolonged fall.

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