EFFECTS OF DECASERpine ON THE CONTENT OF CATEChOLAMINE IN THE BRAIN, ATRIUM AND ADRENAL GLAND OF RABBIT

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One of the side actions which restrict the clinical use of reserpine is a strong and long-lasting mental depression. Looking for other reserpine-like alkaloids less toxic and more useful for clinical trials than reserpine, Velluz et al. (1, 2) have presented 10-methoxydeserpidine (decaserpine), an isomer of reserpine.

The pharmacological effects of decaserpine have been reported in detail by Mir and Lewis (3). When the initial blood pressure of an anesthetized cat was considerably high, the intravenous injection of decaserpine caused a gradual fall and bradycardia, and increased the pressor responses to adrenaline and noradrenaline. The intraperitoneal injection of 20 mg/kg of decaserpine did cause neither ptosis, diarrhea nor sedation in rats. In mice, however, the intraperitoneal injection of 40 to 80 mg/kg of decaserpine induced drowsiness and decrease of spontaneous motor activity in a similar manner to the appropriate dose of reserpine.

On the other hand, Leroy and Schaepdryver (4) have reported that the intraperitoneal injection of 25 mg/kg of decaserpine did not affect the content of catecholamine in the brain and heart of cat 24 hours after the injection. In the previous report (5), the authors studied the time course of the depletion of noradrenaline in the brain and atrium, and of adrenaline in the adrenal glands of rabbit induced by the intravenous or intracarotid injection of reserpine.

In this report, the effects of the intravenous and intracarotid injections of decaserpine on the content of noradrenaline and adrenaline in the tissues were likewise studied in rabbits. Besides, the same effects of tetrabenazine which has been reported to deplete less catecholamine from the peripheral organs than from the brain (6, 7), and of xylopine which has been reported to show weak sedation and a considerably strong adrenolytic action in a variety of animals (8) were studied.

METHODS

Intact albino rabbits, weighing 2.0 to 2.5 kg, were used, without regard to sex. At
the predetermined time after the injection of the test drugs, the animal was killed by cutting both common carotid arteries. Immediately thereafter, the brain, heart and adrenal glands were extirpated. The connective tissues were cleared off from the extirpated organs after they were washed in Ringer's solution and the solution adherent was removed by pressing them between two sheets of filter paper. The organ was then weighed and homogenized in ice-cooled 0.4 N perchloric acid. The homogenate was left in a refrigerator for 2 to 24 hours and then centrifuged. The supernatant of the centrifugate was treated following the method of Bertler and Carlsson (9), and the content of noradrenaline or adrenaline was assayed fluorometrically following the method of Euler and Floding (10).

Decaserpine was dissolved in a dilute solution of acetic acid (1:10–100). Tetrabenazine was used in a form of commercial solution “Rubigen” (Eisai Co.) which contained 25 mg of the alkaloid per ml. Xylopinine citrate was used as one per cent solution. These drugs were injected into the marginal vein of ear, or the bilateral common carotid arteries. For the administration of tetrabenazine, care was taken to inject the drug solution at a rate of 0.1 ml per minute.

Preliminary studies on the normal content of noradrenaline and adrenaline in 5 intact rabbits gave the following figures. The content of noradrenaline in the whole brain was $0.167 \pm 0.026 \mu g/g$, noradrenaline in the atrium was $1.35 \pm 0.32 \mu g/g$ and adrenaline in the adrenal glands was $121 \pm 37 \mu g/2$ glands. These figures agreed well with or somewhat smaller than those reported previously (5).

RESULTS

I. Effects of Decaserpine

Though the intravenous injection of 1.0 to 5.0 mg/kg of decaserpine in rabbits did not induce any behavioral changes within 24 hours after the injection, 10 mg/kg induced a miosis and a respiratory depression. The slight miosis developed soon after the injection of the drug and dissipated within 2 hours thereafter. The depression of the spontaneous respiration especially, in rate developed gradually. Two to three hours after the injection of 10 mg/kg of decaserpine, the respiratory rate decreased to about one half of that before the injection. The intravenous injection of 30 mg/kg of the drug induced a little stronger effect than that of 10 mg/kg and induced a ptosis and a slight depression in motor activity. However, in the dose range studied, there were never observed fall in body temperature and diarrhea. One of the animals which received 30 mg/kg of decaserpine died of a marked depression of the respiratory rate and a clonic convulsion.

As is shown in Table 1, the intravenous injection of 1.0 mg/kg of decaserpine reduced the content of atrial noradrenaline markedly. Three hours after the injection, the level of the atrial amine reduced to one-third of the normal level, while noradrenaline in the brain decreased only 20%. Twelve hours after the injection of 3.0
mg/kg of decaserpine, the atrial amine showed normal content, while the brain amine showed some decrease. Three hours after the intravenous injection of 10 mg/kg of decaserpine, the content of noradrenaline in the brain and atrium and of adrenaline in the adrenal glands showed marked decrease. A marked decrease of the amine in the tissues was also observed in the animal which received 30 mg/kg of decaserpine intravenously. From the results it was shown that decaserpine depleted not only the peripheral catecholamine but also the central noradrenaline, and that the time course of the depletion of catecholamine somewhat differed between the brain and the peripheral organs such as atrium and adrenal glands. Accordingly, the more detailed study on the depletion of catecholamine by decaserpine was carried out in rabbits.

**TABLE 1. Tissue catecholamine content in percentage after administration of decaserpine, tetrabenazine or xylopinine in rabbit.**

<table>
<thead>
<tr>
<th>Dose and Route</th>
<th>Time</th>
<th>Brain Noradrenaline</th>
<th>Atrium Noradrenaline</th>
<th>Adrenal Glands Adrenaline</th>
<th>Number of Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decaserpine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v. 1 mg/kg</td>
<td>3h</td>
<td>83%</td>
<td>32%</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>12h</td>
<td>79%</td>
<td>103%</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>3h</td>
<td>37%</td>
<td>4%</td>
<td>21%</td>
<td>2</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>30m</td>
<td>35%</td>
<td>64%</td>
<td>42%</td>
<td>died</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>2h</td>
<td>16%</td>
<td>30%</td>
<td>24%</td>
<td>1</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>3h</td>
<td>41%</td>
<td>7.8%</td>
<td>70%</td>
<td>2</td>
</tr>
<tr>
<td>i.a. 0.5 mg/kg</td>
<td>30m</td>
<td>42.5%</td>
<td>36%</td>
<td>38.5%</td>
<td>died</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>2h</td>
<td>51%</td>
<td>47%</td>
<td>19%</td>
<td>1</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>30m</td>
<td>55%</td>
<td>52%</td>
<td>34%</td>
<td>died</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>1h</td>
<td>42%</td>
<td>49%</td>
<td>41%</td>
<td>died</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>i.v. 50 mg/kg</td>
<td>3h</td>
<td>14.3%</td>
<td>26.8%</td>
<td>66%</td>
</tr>
<tr>
<td>Xylopinine</td>
<td>i.v. 5 mg/kg</td>
<td>3h</td>
<td>88%</td>
<td>75%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg</td>
<td>3h</td>
<td>110%</td>
<td>90%</td>
<td>-</td>
</tr>
</tbody>
</table>

h = hours, m = minutes

**FIG. 1. Percentage change of catecholamine content of the brain, atrium and adrenal glands in rabbit in response to decaserpine.**

5 mg/kg i.v. 0.1 mg/kg i.a.
- - - - - Brain
- - - - Atrium
- - - - - Adrenal Glands

The time course of the depletion of adrenaline in the brain, atrium and adrenal glands by the intravenous
injection of 5.0 mg/kg of decaserpine is shown in Fig. 1. The percentage values of the content of noradrenaline or adrenaline to the normal content at 1, 2, 3 and 12 hours after the injection of the drug are plotted. The decrease of noradrenaline in the brain and atrium and of adrenaline in the adrenal glands developed almost similarly. The marked decrease was obtained 2 to 3 hours after the injection. The atrium seemed to be most sensitive to decaserpine alike to reserpine (9, 11, 12). The content of the amine in these tissues recovered considerably 12 hours after the injection. In Fig. 2, the time course of the depletion of the amine in the tissues caused by the intravenous injection of 1.0 mg/kg of reserpine is shown. The depleting effect of reserpine was long-lasting, while that of decaserpine was short-lasting.

The intracarotid injection of 5.0 mg/kg of decaserpine killed the animal within 30 minutes to 1 hour after the injection. The animal showed a marked depression of the respiratory rate and clonic convulsions before death. The autopsy studies revealed the marked dilation and the diastolic standstill of the heart. Besides, the marked inflation of lungs and intestine was observed. The cause of death by the intracarotid injection of decaserpine might have been the respiratory failure and diastolic standstill of the heart.

At the time of death of the animal which received 5.0 mg/kg of decaserpine intracarotidally, the content of noradrenaline in the brain and atrium and of adrenaline in the adrenal glands showed marked decrease. The intracarotid injection of 0.5 mg/kg of the drug also sometimes killed the animal and decreased profoundly the amines in the tissues. The marked decrease of the amine was already observed 30 minutes after the injection. The injection of the solvent of reserpine or dilute solution of acetic acid did not induce any sign of behavioral changes or changes in level of catecholamine in the tissues studied. For the detailed study, the time course of the depletion of catecholamine was studied in the rabbit which received 0.1 mg/kg of decaserpine intracarotidally.

The time courses of the depletion of noradrenaline in the brain and atrium, and of adrenaline in the adrenal glands of rabbits which were injected intracarotidally 0.1 mg/kg of decaserpine, and of reserpine are illustrated in Figs. 1 and 2. All the animals survived at the time of the sacrifice. The content of catecholamine in the tissues

Fig. 2. Percentage change of catecholamine content of the brain, atrium and adrenal glands in rabbit in response to reserpine.
decreased slightly. The decrease of noradrenaline in the brain and atrium caused by decaserpine was 30 to 40% of the normal content at 1 hour after the injection and, thereafter, the content of the amine recovered gradually. On the other hand, the content of adrenaline in the adrenal glands decreased progressively. Twelve hours after the injection, a considerable decrease of the amine was still observed. As is shown in Fig. 2, the intracarotid injection of reserpine decreased the content of catecholamine in all the tissues tested and the reduction of the amine was long-lasting.

From the results described above, it was suggested that the toxic effect of the intracarotid injection of decaserpine was not correlated with the decrease of catecholamine in the central nervous system.

II. Effects of Tetrabenazine and Xylopinine

The intravenous injection of 50 mg/kg of tetrabenazine induced a profuse salivation, marked and prolonged ptosis and sedation in rabbits. The decrease of catecholamine was considerably stronger in the brain than in the atrium or adrenal glands. The results are shown in Table 1. This stronger reduction of the brain amine caused by tetrabenazine agrees well with the results presented by Quinn et al. (6) and Pletscher et al. (7), but the reduction of noradrenaline in the atrium and of adrenaline in the adrenal glands demonstrated in this experiment differs from the conclusion obtained by Brodie et al. (13) who denied the depletion of the catecholamine in the peripheral tissues except the adrenal glands by tetrabenazine.

The intravenous injection of 10 to 30 mg/kg of xylopinine induced a short-lasting sedation, ptosis, decrease of the spontaneous motor activity and dilatation of the pupils. However, the chemical assay of noradrenaline in the brain and heart of the animal which had received 5 and 10 mg/kg of xylopinine did not show significant change of the amine content.

DISCUSSION

The intravenous injection of 10 to 30 mg/kg of decaserpine evoked a slight miosis and a marked depression of the respiratory rate in rabbits. The ptosis and motor sedation which were demonstrated in mice injected 40 to 80 mg/kg of decaserpine (3) were also observed in rabbits received 30 mg/kg of decaserpine. The intravenous injection of the dose less than 5 mg/kg of the drug did not evoke any significant behavioral changes. On the other hand, the intracarotid injection of 5 mg/kg of decaserpine killed the animal by the marked depression of the spontaneous respiration and the clonic convulsion. The autopsy studies showed that the heart stopped at the diastole and the lungs and the small intestine were extremely inflated as if air was injected. Sometimes, the minute dose of decaserpine (0.5 mg/kg) also killed the animal. The intracarotid injection of the solvent of decaserpine did not cause any effect. Accordingly, the death of the animal may have been derived from the direct effect of the drug on the central nervous system. The death of mice due to respiratory failure
after decaserpine has been postulated by Mir and Lewis (3). The depression of the respiratory rate and the appearance of the clonic convulsion as well as the marked inflation of the lungs observed in the present experiment also support this finding. However, the administration of decaserpine in either route did not induce any fall in body temperature or diarrhea.

The intravenous injection of decaserpine decreased not only the level of noradrenaline in the atrium, and of adrenaline in the adrenal glands, but also the level of noradrenaline in the brain. The decrease of brain noradrenaline in response to 5 mg/kg of decaserpine was already observed 30 minutes after the injection and the reduction to 40% of the normal content was obtained 2 to 3 hours after the injection. Twelve hours after the injection, there was still observed a considerable decrease of the brain amine.

The intracarotid injection of 0.1 mg/kg of decaserpine also decreased slightly the level of noradrenaline in the brain. Compared with the similar effect of the same dose of reserpine, the effect of decaserpine was weak and short-lasting. The slight depletion of noradrenaline in the brain caused by decaserpine may show that the strong toxic effect of the intracarotidally injected decaserpine does not correlate with the depletion of brain noradrenaline. The fact that the large dose (30 mg/kg) of decaserpine injected intravenously did not exhibit strong toxic effect suggests that the intravenously administered decaserpine may have hardly passed through the blood-brain barriers or, with more possibility, that it may have been transformed into metabolites, which have no toxic effect on the brain.

The intravenous injection of 5 mg/kg of decaserpine decreased the level of noradrenaline in the atrium. The effect was already observed 30 minutes after the injection and the reduction to 20% of the normal content was obtained 3 hours after the injection. The intracarotid injection of 0.1 mg/kg of decaserpine also decreased the level of noradrenaline in the atrium, but the effect was much weaker than that of the same dose of reserpine.

The level of adrenaline in the adrenal glands was also decreased by the intravenous injection of decaserpine. The time course of the decrease of the amine was closely similar to that of noradrenaline in the brain and atrium. The long-lasting depletion of the amine in the peripheral tissues may correlate with the long-lasting hypotensive effect of reserpine or decaserpine (3, 14-16). The lack of the sedative effect of the intravenous dose of 5 mg/kg of decaserpine, which decreases the brain amine considerably, strongly excludes the possibility that the central depression may be indispensable for the manifestation of the hypotensive effect of decaserpine or even reserpine. The similar conclusion has been presented by Peterfalvi and Jequier (17). However, the possibility that the sedative effects of reserpine and decaserpine correlate with depletion of noradrenaline in the brain remains still to be settled, because the intravenous injection of large dose of decaserpine induces the depletion of noradrenaline in the brain with a slight sedation. The depletion of adrenaline in the adrenal glands in
response to the intracarotid injection of 0.1 mg/kg of decaserpine developed gradually, and 12 hours after the injection there was considerably strong decrease of the amine. Whether the long-lasting decrease of adrenaline in adrenal glands correlates with the hypotensive effect of decaserpine is open to further studies.

SUMMARY

The effects of the intravenous or intracarotid injection of decaserpine on the contents of noradrenaline in the brain and atrium, and of adrenaline in the adrenal glands were studied in the unanesthetized rabbit.

1. The intravenous injection of decaserpine depleted not only noradrenaline in the heart and adrenaline in the adrenal glands but also noradrenaline in the brain. The time courses of the depletion of the amines in these organs were similar.

2. The intracarotid injection of decaserpine also depleted noradrenaline and adrenaline slightly. The depletion of the amines caused by 0.1 mg/kg of decaserpine was less and shorter lasting than that caused by the same dose of reserpine.

3. Large dose of the intravenous decaserpine depressed the respiratory rate markedly and induced a slight sign of sedation and ptosis. Moderate dose of the intracarotid decaserpine often killed the animal due to the respiratory failure and convulsion.

4. The intravenous injection of tetrabenazine depleted not only noradrenaline in the brain but also noradrenaline in the atrium and adrenaline in the adrenal glands. The intravenous injection of xylopinine did not significantly affect the levels of the amines in these organs.

REFERENCES

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