STUDIES ON THE HYPOTENSIVE ACTION OF DIHYDRO-
ERGOKRYPTINE (DHK) AND EPINEPHRINE-
REVERSAL IN THE DOG AND CAT

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Recently, two important steps in pharmacology on the partial synthetized derivatives of ergot alkaloids were made by a group of investigators in Switzerland. One was the hypotensive action of the hydrogenated alkaloids of the ergotoxine group and the other was the psychogenic or hallucinogenic action of lysergic acid diethylamide (LSD).

The hydrogenated alkaloids of ergotoxine which is composed of three alkaloids (ergocristine, ergocornine and ergokryptine), differ from the natural alkaloids in being much less toxic and in having a hypotensive activity. The hypotensive action was due to mainly central origin and partly peripheral adrenolytic action, but they have a slight vasoconstrictor action upon the peripheral blood vessels (Hoobler and Dontas, 1953 (1)). Konzett and Rothlin (1953) (2) reported some analytical results on the site of action of the hydrogenated ergot alkaloids and the pathways conducting vasodilator impulses from the brain centers. Previously, Rothlin (1949) (3) demonstrated that the hypotensive action of these alkaloids is markedly influenced by peripheral vascular tone in his spinal cat experiments.

This report is concerned with: 1) the quantitative investigation of the blood pressure response and bradycardic and adrenolytic effects of DHK in the dog under two kinds of anesthesia, 2) the mode of action of the hypotensive action of DHK and the epinephrine-reversal induced by DHK in the intact and spinal cat, with special references to the relation between the vasotone and the two responses.

MATERIALS AND METHODS

DHK in its base form was supplied by Dr. Abe of the Takeda Fermentation Research Laboratory. He and his collaborators (1952, 1955) (4) obtained DHK by hydrogenation of ergokryptine which they had isolated from the saprophytic cultivation of a certain ergot fungus. The base is readily soluble in 0.1% tartaric acid solution.

Mongrel dogs weighing 10–13 kg and cats weighing 2–3 kg were used. The anesthetics used are given in the text. Arterial blood pressure was recorded on a smoked drum through mercury manometer from a canulated femoral or carotid artery and respiration was simultaneously recorded from pneumograph.

The technique of decapitation was followed by the method previously reported by Kumagai, Yui, Ogawa, Ohga and Sakuma (1953) (5).
RESULTS

The blood pressure response and bradycardic and adrenolytic activities of DHK in the dog under two kinds of anesthesia

The action of DHK on blood pressure and the adrenolytic effect were quantitatively tested under the two kinds of anesthesia: one was induced with 1.0 mg/kg of morphine sulfate s.c. and 1.3 g/kg of urethane s.c., and the other with 30 mg/kg of sodium thiopental i.v. and 100 mg/kg of sodium barbital i.p.. In the intravenous dose of 50 µg/kg of DHK, the blood pressure response, bradycardic activity and inhibitory effect on the vasopressor response by 2.5 µg/kg of epinephrine before and after administration of the agent were respectively investigated.

<table>
<thead>
<tr>
<th>Anesthesia</th>
<th>Exp. No.</th>
<th>Mean blood pressure and epinephrine response (mmHg)</th>
<th>Heart rate (/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After 10 min</td>
</tr>
<tr>
<td>Morphine-urethane</td>
<td>1</td>
<td>98 (48)</td>
<td>88 (28)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>92 (30)</td>
<td>66 (10)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>92 (40)</td>
<td>74 (20)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>130 (32)</td>
<td>124 (22)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>114 (34)</td>
<td>98 (16)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>105.2 (36.8)</td>
<td>90 (19.2)</td>
</tr>
<tr>
<td>Thiopental-barbital</td>
<td>1</td>
<td>130 (32)</td>
<td>158 (32)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>140 (58)</td>
<td>144 (62)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>132 (40)</td>
<td>140 (38)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>134 (46)</td>
<td>124 (42)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>158 (32)</td>
<td>170 (60)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>138.8 (45.6)</td>
<td>147.2 (60)</td>
</tr>
</tbody>
</table>

Mean blood pressure and heart rate were compared before and after intravenous administration of 50 µg/kg of DHK.

( ): a rise of blood pressure caused by intravenous injection of 2.5 µg/kg of epinephrine hydrochloride.

The results obtained in 10 experiments are summarized in Table 1, and the typical examples are shown in Figure 1. It is of great interest that quite different responses on blood pressure were produced under the two kinds of anesthesia respectively. Namely, blood pressure was depressed for a long time under morphine-urethane anesthesia. But under thiopental-barbital anesthesia there was, to the contrary, a temporary rise in blood pressure. Similar reactions were observed not only under thiopental-barbital anesthesia but also under the anesthesia by the other barbiturates such as pentobarbital. As the elevation in blood pressure was not recognized under urethane-chloralose anesthesia without morphine, it seems that these barbiturates may play a specific role in the hypertensive reaction of DHK.

On the heart rate, DHK showed a greater inhibitory action under thiopental-barbital anesthesia than under morphine-urethane anesthesia.
The mode of the hypotensive action of DHK in the intact and spinal cat

In the urethanized (1.3 g/kg s.c.) cat, DHK in the dose of 0.1 mg/kg i.v. caused a definite and prolonged fall of blood pressure and reversed the vasopressor action of epinephrine (5 µg/kg i.v.) starting immediately after administration of DHK. The hypotensive action could be confirmed even when the initial level of blood pressure had been lowered to about 40 mm Hg by bleeding. Bilateral vagotomy reduced this action of DHK to some extent and moreover atropine sulfate in the dose of 0.5–2.0 mg/kg i.v. abolished it almost completely. During intravenous infusion of TEAB (0.5 mg/kg/min) or after pretreating with hexamethonium iodide (5 mg/kg i.v.), DHK showed an abrupt rise of blood pressure.

In the spinal cat whose blood pressure was definitely lowered by exclusion of central vasoconstriction, DHK produced a remarkable rise of blood pressure by its direct vasoconstrictor action on peripheral vascular beds which had been masked by the centrogenic vasodepression in the intact animal. The vasopressor action of DHK in the spinal cat was still observed while the blood pressure maintained at a normal level by continuous infusion of pituitrin or pitressin. On the contrary, it was shown that DHK produced a prolonged decrease in blood pressure during infusion of epinephrine as an agent to maintain vascular tone.

Epinephrine-reversal induced by DHK

The epinephrine-reversal was almost unaffected by pretreatment of atropine or ganglion blockades and bilateral vagotomy in the intact urethanized cat. Under low level of blood pressure, however, the reversal disappeared and epinephrine produced only normal pressor
response in the cats bled or decapitated. On the other hand, the reversal was demonstrated in both cases of the intact and spinal cat so long as blood pressure was maintained at the normal level. Therefore, the generation of this reversal is independent of whether CNS is kept intact or not, and also independent of atropinization and ganglion blockade.
DISCUSSION

The different responses of DHK under the two kinds of anesthesia

The adrenolytic action of ergot alkaloids is markedly reduced by barbiturates and this reduced action may explain the apparently enhanced sympathomimetic pressor responses induced by ergot alkaloids under the anesthesia (Nickerson, 1949 (6)). Basically, the hydrogenated ergot alkaloids contract peripherally the musculature of arterial walls as same as the natural alkaloids do. Accordingly, as the contracting action of DHK is enhanced to a large extent by barbiturate and it overcomes the central action, it may show a transient hypertensive action under barbiturate anesthesia. Similar phenomena were observed in the isopropylarterenol-reversal induced by ergotamine. This reversal was well established under barbiturate anesthesia as reported by Lands and his co-workers (1950) (7), but not under urethane anesthesia (Yui and Takeo, 1957 (8)). Under the two kinds of anesthesia there is a definite difference between the patterns of blood pressure which epinephrine causes in normal or ergotaminized animals.

According to Ngai and Wang (1955) (9), the dose of Hydergine (an equal portion mixture of dihydro-derivatives of ergotoxine group) required to block completely the pressor action of intravenously injected epinephrine, is presumed to be about 0.2 mg/kg. In the dose of DHK used (50 µg/kg), only a partial block of epinephrine was found under the two kinds of anesthesia in the dog.

The relation between the vascular tone and the hypotensive action of DHK or epinephrine-reversal

The hypotensive action of DHK is blocked partly by vagotomy or almost completely by atropinization, and reversed by destruction of CNS or ganglion blockade. It is, however, produced as long as the CNS and the efferent pathways are kept intact even when the blood pressure of animal is suppressed at low level. The fact that DHK produces the slowing of the heart rate suggests the excitation of the vagal center, as reported by Baumann, Jerran and Scager (1954) (10). It is presumed that the cholinergic mechanisms may be concerned to a great extent in the conduction of a vasodepressor and cardiac-inhibitory impulses produced by DHK, as judged by the fact that vagotomy and atropinization depress or abolish the action of the agent.

It is confirmed that a fall of blood pressure by hydrogenated ergot alkaloids which Rothlin observed in the spinal cat during the infusion of epinephrine, is not due to the result of elevation of vasotone, but to their adrenolytic property which manifests itself very rapidly and strongly after administration of the hydrogenated alkaloids. Because in a high level of blood pressure by infusion of pituitrin, the hydrogenated ergot alkaloid produced by no means a hypotensive reaction and showed a slight rise of blood pressure.

There have been many hypotheses on epinephrine-reversal, in regard to whether or not it is originated centrally or peripherally. Tayler and Page (1951) (11), Britton and Ahlquist (1952) (12) and Yui (1954) (13) reported respectively that epinephrine reduced centrally the systemic blood pressure, when the dog's head was kept separated from its
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body except for the unbroken connection of the vagus and spinal cord. But according to the results obtained, it is conjectured that one of the most essential factors for the generation of the reversal by DHK may be the maintenance of the blood pressure at a high level.

SUMMARY

DHK produces a definite fall of blood pressure under morphine-urethane anesthesia but a transient elevation under thiopental-barbital anesthesia in the dog. In the latter case it is presumed that the reaction may be due to the potentiation of its peripheral pressor action by barbiturate.

The following conclusions are reached by the results of four groups of experiments i.e. at normotensive or hypotensive state in the intact and spinal cat. The hypotensive action of DHK is produced by means of alive brain and its intact efferent pathways which may contain ganglion and cholinergic fibers. On the other hand, the epinephrine-reversal induced by DHK can be demonstrated regardless of the brain centers and of its efferent pathways as long as arterial blood pressure is maintained at a sufficiently high level.

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