EFFECT OF BRETYLIUM AND GUANETHIDINE ON THE HYPERGLYCAEMIC ACTION OF ADRENALINE

By

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The effect of bretylium and guanethidine on the hyperglycaemic action of adrenaline was studied in 18 hr fasted rabbits. Both the drugs potentiated the hyperglycaemic action of adrenaline in doses which did not have any effect on fasting blood glucose level. In higher doses guanethidine elicited an hyperglycaemic effect of its own. The results are discussed.

Two new antihypertensive drugs, bretylium and guanethidine have recently been introduced in therapeutics. These drugs produce a gradual, lowering of arterial blood pressure in animals and man, probably through a specific blocking action on the peripheral adrenergic neurone (Boura and Green, 1959; Maxwell et al., 1959). Guanethidine in addition causes a depletion of the tissue stores of noradrenaline (Sheppard and Zimmerman, 1959).

Bretylium and guanethidine have been shown to potentiate the excitatory and inhibitory effects of catecholamines on blood pressure, nictitating membrane, heart, uterus and bronchial smooth muscle both in vivo and in vitro (Gokhale & Gulati, 1961; Page and Dustan, 1959). A sensitization of the peripheral effector cells to the action of catecholamines has been suggested as a probable explanation for this potentiation (Gokhale & Gulati, 1961). The effect of bretylium and guanethidine on the glycogenolytic (hyperglycaemic) action of adrenaline has not so far been investigated. The present communication describes the effect of these drugs on the hyperglycaemic action of adrenaline in rabbits.

METHODS

White rabbits of either sex, weighing between 1.25 to 2 kg were used as experimental animals. All animals were fasted for 18 hr before taking up for experiment and the fasting blood glucose level was determined in each case.

In a few preliminary experiments the effects of bretylium and guanethidine on fasting blood glucose level was studied with a view to determine suitable doses which by themselves would not alter the blood glucose level.
## Table

*Modification of the hyperglycaemic action of adrenaline by bretylium and guanethidine*

<table>
<thead>
<tr>
<th>Time interval after adrenaline injection in min.</th>
<th>Bretylium 5 mg/kg</th>
<th>Guanethidine 1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean per cent increased in blood glucose level with S.E. of mean</td>
<td>Mean per cent increased in blood glucose level with S.E. of mean</td>
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<tr>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>13.3 ± 2.9</td>
</tr>
<tr>
<td>40</td>
<td>6</td>
<td>25.0 ± 5.0</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>41.6 ± 5.9</td>
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<tr>
<td>90</td>
<td>6</td>
<td>30.5 ± 4.1</td>
</tr>
<tr>
<td>120</td>
<td>6</td>
<td>15.8 ± 4.1</td>
</tr>
</tbody>
</table>

* a: No of experiment  
  b: Values from control animals  
  c: Values from treated animals  
  d: p of difference from control values
In potentiation studies the animals were divided in two groups of 3 animals each. One group received 15 μg/kg of adrenaline intraperitoneally; the other in addition, received an intraperitoneal injection of 5 mg/kg of bretylium given 30 min before the challenging dose of adrenaline. Blood samples were collected from the marginal ear vein at 20, 40, 60, 90 and 120 min intervals. Blood glucose was estimated by the method of Folin and Malmros (1929). After one week the two groups were crossed over.

In another set of similarly planned experiments 1 mg/kg of guanethidine was substituted in place of bretylium.

RESULTS

Effect of bretylium and guanethidine on fasting blood glucose level.—On intraperitoneal injection in rabbits doses of 2.5 mg/kg, 5 mg/kg and 10 mg/kg of bretylium did not alter the fasting blood glucose level at 20, 40, 60, 90 and 120 min intervals. 2 mg/kg and 5 mg/kg of guanethidine injected intraperitoneally appreciably increased the fasting blood glucose level especially at the 20 and 40 min intervals; a dose of 1 mg/kg had no effect on the fasting blood glucose level.

In view of the above findings the modification of the hyperglycaemic action of adrenaline was studied against doses of 5 mg/kg of bretylium and 1 mg/kg of guanethidine.

Modification of the hyperglycaemic action of adrenaline by bretylium and guanethidine.—5 mg/kg of bretylium markedly potentiated the hyperglycaemic action of adrenaline at 20 and 40 min intervals; the per cent rise of blood glucose at 90 and 120 min intervals, was however, below the control values. 1 mg/kg of guanethidine potentiated the hyperglycaemic action of adrenaline especially at 90 and 120 min intervals (Table).

DISCUSSION

Adrenaline and other adrenergic drugs elicit a variety of diverse responses from the smooth muscle structures in the body. Thus adrenaline produces a contraction of the vascular smooth muscle, the muscle of the splenic capsule, the nictitating membrane and the radial muscle of the iris but causes a relaxation of bronchial, intestinal and in some species the uterine smooth muscle. To rationalise these facts it is commonly accepted that adrenaline and other adrenergic drugs act through a specialized receptor mechanism known as the adrenergic receptor. Roughly speaking, the excitatory responses are said to be subserved by the alpha adrenergic receptor while the beta recep
tor is associated primarily with inhibitory responses (Ahlquist, 1948). The various excitatory and inhibitory effects of catecholamine have been shown to be potentiated by bretylium and guanethidine probably through a sensitization of the adrenergic receptors to the action of catecholamines (Gokhale and Gulati 1961; Page and Dustan, 1959). In addition to these muscular actions, a variety of metabolic effects is attributed to the catecholamines. The one that has received the most emphasis is the stimulation of glycogenolysis as a consequence of the activation of glycogen phosphorylase in various tissues (Sutherland and Cori, 1951; Cori and Illingworth, 1956; Hess and Haugaard, 1958.)

The glycogenolytic effect of adrenaline results in an increase in blood glucose. The results of our experiments have shown that both bretylium and guanethidine potentiate the glycogenolytic or hyperglycaemic action of adrenaline.

The exact receptor status of the glycogenolytic action of adrenaline is still uncertain. Furchgott (1959) has postulated a separate receptor called the gamma receptor for the glycogenolytic action of adrenaline. If this postulate is true, then it would seem that the sensitizing action of bretylium and guanethidine extends to this receptor also.

Bretylium and guanethidine produce a gradual lowering of arterial blood pressure; part of the observed potentiation of injected adrenaline might be due to the additive effect of endogenous adrenaline secreted as a consequence of this hypotension.

The intestinal smooth muscle relaxation produced by adrenaline is not completely blocked either by phenoxybenzamine or dichloro-isoprenaline. On the basis of this, Furchgott (1959) has postulated an additional delta receptor for this function of adrenaline. It would be interesting to see if the delta receptor is also sensitized by bretylium and guanethidine. In fact guanethidine does potentiate the relaxant action of adrenaline on the rabbit ileum (Gokhale and Gulati, unpublished observations).

In higher doses (2 and 5 mg/kg) guanethidine itself exerts a hyperglycaemic action. This is not entirely unexpected as this drug has been shown to have adrenergic effects on blood pressure, heart, nictitating membrane and uterus (Gillis and Nash, 1961; Gokhale, Gulati and Kelkar, 1963). This direct hyperglycaemic action of guanethidine coupled with its property of potentiating the hyperglycaemic action of adrenaline might result in an in-
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techolamines (Gokhale and to these muscular actions, catecholamines. The one
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crase in insulin requirement in diabetic patients who are simultaneously receving guanethidine for their hypertension.

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REFERENCES


