THE INFLUENCE OF DIHYDROERGOTAMINE, HYDERGIN AND HEXAMETHONIUMCHLORIDE ON THE COURSE OF THE BLOODSUGAR LEVEL DURING THE FIRST HALF HOUR AFTER ALLOXAN INJECTION

By

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In a previous publication from this laboratory (Gaarenstroom & Siderius, 1954) the hypothesis was brought forward that under normal circumstances the tendency of the bloodsugar level to decrease immediately after intravenous injection of alloxan can partly or completely be obscured by a tendency of this level to increase. A number of possible reasons for this increase have been discussed in the review by Lukens (1948), one of them being the secretion of adrenaline by the adrenals, which causes a mobilisation of liver glycogen. Recent experiments (Gaarenstroom & Rümke, 1955) have supported the view that this tendency of the bloodsugar level to increase after alloxan injection can partly be explained by the ether anaesthesia used. Adrenaline may also be responsible for this effect, as Braunsteiner et al. (1952) have found that the increase in the bloodsugar level after ether anaesthesia can be prevented by a sympathicolytic drug. In order to investigate whether, in the absence of ether anaesthesia, the alloxan induced increase of the blood sugar is partly or completely mediated by adrenaline, the effect of pretreatment with dihydroergotamine (D. H. E.), hydergin and hexamethonium chloride has been studied.

Rothlin (1946) has shown that dihydrogenated ergot alkaloids exert an inhibitory effect on the adrenaline induced hyperglycemia. In our first experiment we determined whether D. H. E. enhances the fall in bloodsugar level during the first half hour following alloxan injection. However, D. H. E. causes a vasoconstriction which makes it difficult to take blood samples from the tail and Cosgrove (1954) has found that the vasoconstriction caused by

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ergotaminetartrate can influence the blood sugar levels. Hence pretreatment with the vasodilating hydergin (a mixture of equal parts of dihydroergocornine, dihydroergokryptine and dihydroergocristine) was used in later experiments.

Hexamethonium increases the sensitivity to insulin in man and unanaesthetized dogs. This is presumably the result of the ganglion blocking action of hexamethonium, which prevents a compensatory sympathetic activity in response to hypoglycemia (Schachter, 1951; Laurence & Stacey, 1952). The influence of pretreatment with hexamethonium on the bloodsugar after alloxan injection has also been studied, as a prevention of a sympathetic discharge could be assumed to enhance the decrease of the bloodsugar level. The effectiveness of the given doses of hexamethonium was tested in a control experiment.

MATERIAL AND METHODS

Female white rats of an inbred strain weighing 100-150 gm. (in pairs with a small weight range) were used in the experiment. The rats were fasted for about 16 hours prior to pretreatment.

The pretreatment consisted of intraperitoneal injection of either 0.1 mg. D. H. E. in 1 ml. saline, 0.03 mg. hydergin in 1 ml. saline or 3 mg. hexamethoniumchloride in 0.5 ml. saline. After 10-30 min. alloxan or a corresponding amount of saline was injected into one of the tailveins. 40 mg. alloxan/kg. from a one per cent solution was administered.

Blood samples for the determinations of the sugar level were taken from the tail immediately before and 30 min. after alloxan injection. Bloodsugar was estimated according to Hagedorn and Jensen as modified by Fujita & Okamato (1930).

In a control experiment the rats were pretreated with hexamethonium and saline alternatively and all animals received an alloxan injection after 10-30 min.

The differences between the bloodsugar value 30 min. after and just before injection in alloxan and saline injected rats have been compared and statistically analysed. The probability (p) that the decrease of the bloodsugar in an alloxan injected is larger than that in the saline injected partner has been tested with Wald's sequential probability ratio test (Wald, 1947, p. 90), in which for $p_0 = 0.55$; $p_1 = 0.85$; $\alpha = 0.05$; $\beta = 0.05$ has been chosen. In the control experiment the probability that the decrease of the bloodsugar in a hexamethonium pretreated animal is larger than that in the saline injected partner was tested in the same way.

RESULTS

These have been summarized in Table 1. In D. H. E. as well as in hydergin and hexamethonium pretreated animals the probability that the decrease in the blood sugar value of alloxan injected animals was larger than that in the saline injected partners was found to be smaller than 0.55. This means that the significance of sympathetic activity for a tendency of the bloodsugar level to increase after alloxan injection is not very important.
Table 1.
Average bloodsugar values immediately before (0) and 30 min. after injection, and their difference (d) in mg. per 100 ml. n = the number of pairs which were needed to bring the sequential probability ratio test to an end.

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Treatment</th>
<th>0</th>
<th>30</th>
<th>d</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. H. E.</td>
<td>Alloxan</td>
<td>85.5</td>
<td>81.9</td>
<td>-3.6</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>87.7</td>
<td>78.3</td>
<td>-9.4</td>
<td></td>
</tr>
<tr>
<td>Hydergin</td>
<td>Alloxan</td>
<td>85.1</td>
<td>90.4</td>
<td>+5.4</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>86.1</td>
<td>86.6</td>
<td>+0.5</td>
<td></td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>Alloxan</td>
<td>85.7</td>
<td>78.3</td>
<td>-7.4</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>84.3</td>
<td>77.6</td>
<td>-6.7</td>
<td></td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>Saline</td>
<td>78.6</td>
<td>68.1</td>
<td>-10.5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Alloxan</td>
<td>79.6</td>
<td>98.7</td>
<td>+19.1</td>
<td></td>
</tr>
</tbody>
</table>

In the control experiment the probability that the decrease of the bloodsugar value in hexamethonium pretreated, alloxan injected animals is larger than that in their saline pretreated, alloxan injected partners was found to be larger than 0.85. From the results of this experiment it can be concluded that the dose of hexamethonium was large enough to prevent the sympathetic discharge caused by the experimental procedure, so that the hexamethonium dose used in the other experiment can be assumed to have been large enough to suppress a reaction if such a reaction had been present.

SUMMARY

After pretreatment with dihydroergotamine, hydergin or hexamethonium, intravenous injection of alloxan does not result in a larger decrease of the bloodsugar values in the first half hour than saline injections. This makes it improbable that part of the tendency of the bloodsugar to increase after alloxan administration is of sympathetic origin.

REFERENCES


