Preventive action of phentolamine on adrenaline induced blood glucose elevation in humans

S. Porta, H. M. H. Hofmann, U. Ertl,
I. Rinner, P. Puerstner, P. A. M. Weiss, P. Felsner,
and W. Korsatko

Institut für funktionelle Pathologie,
Geburtshilflich-Gynaekologische Klinik der Universität Graz, Graz, Austria

Abstract. A comparison of the action of adrenaline infusion and a combined adrenaline + alpha blocker (phentolamine, Regitine®) infusion on blood glucose (BG), plasma immunoreactive insulin (IRI), BG/IRI ratio, C-peptide, and plasma cortisol levels was made in healthy young human subjects. The purpose of the experiment was to check, whether alpha block could abolish adrenaline-induced enhancement of blood glucose levels. The results show that during enhanced adrenaline levels, the use of regitine could indeed normalize blood glucose levels, not so much by increasing the IRI secretion, but by diminishing adrenaline-induced liver glycogenolysis via alpha receptors. This could be a model to prevent stress (adrenaline) induced metabolic deviations in diabetics, especially before and during predictable stress situations, e.g. examinations or surgery.

In previous experiments with rats using subcutaneously implanted adrenaline (A) tablets as a controlled release system, we succeeded in maintaining hyperglycemia for 20 h with concomitant relatively suppressed IRI levels. This we called an A-induced diabetes-like reaction (Porta et al. 1984). In spite of these high free A plasma levels, a concomitant alpha blockade in a comparatively low dose prevented hyperglycemia and created hyperinsulinemia for 20 h.

This shows a possible coexistence of normal glucose levels and hyperadrenalinaemia and should open up new approaches in the management of metabolic deviations of mentally excited diabetics by application of alpha blockers.

Therefore the first step to reach this goal, and the aim of the present paper, should be to ascertain the reproducibility in man of those effects already seen in rats.

In rats we observed the full effect until the tablet was removed after 20 h. Since humans could hardly be treated for so long for experimental purposes alone, we had to extrapolate the results of a 90-min infusion.

Subjects and Methods

Nine healthy, fasting male volunteers, age 23.8 years ± 0.9 and body weight 66.3 kg ± 4, were informed of the nature, purpose and possible risks of the study before they gave their consent to participate. Results are presented as mean ± SEM, if not otherwise stated.

Performance of the experiment

Indwelling catheters were placed: 1. In the right antecubital vein for blood sampling. 2. In the left antecubital vein for A and A + phentolamine (Regitine®) (Reg) infusion. 3. In a dorsal vein of the left hand for blood glucose (BG) monitoring with a Biostator Ciba Geigy A.G., Basel, Switzerland.
Table 1.
Experimental approach.

<table>
<thead>
<tr>
<th>Time</th>
<th>Adrenaline group</th>
<th>Adrenaline + Regitine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>–30 min</td>
<td>Preliminary treatment Blood check</td>
<td>Blood check 1 + Regitine bolus + Regitine infusion</td>
</tr>
<tr>
<td>0 min</td>
<td>Start of experiment Adrenaline infusion</td>
<td>Adrenaline infusion</td>
</tr>
<tr>
<td>20 min</td>
<td>Blood check 2</td>
<td>Blood check 2</td>
</tr>
<tr>
<td>60 min</td>
<td>Blood check 3</td>
<td>Blood check 3</td>
</tr>
<tr>
<td>90 min</td>
<td>Blood check 4</td>
<td>Blood check 4</td>
</tr>
<tr>
<td>120 min</td>
<td>Blood check 5</td>
<td>Blood check 5</td>
</tr>
</tbody>
</table>

Doses: A – infusion 1.2 micrograms/min/m². Reg bolus 25 mg/m². Reg infusion 120 micrograms/min/m². (1)–(5): Blood sampling for determination of BG (Beckman glucose analyser), IRI (Phadeseph RIA Pharmacia Uppsala), C-peptide (RIA kit Hoechst), Cortisol (1 Cortisol RIA kit travenal gentech diagnostics). Statistics: t-tests, correlations and analyses of variance were carried out with an Olivetti P 6040 using standard Olivetti software as well as our own t-test software.

Results

1. BG values
A-treatment led to an enhancement of BG in absolute values from 2.90 ± 0.04 mmol/l to a maximum of 7.20 ± 0.44 mmol/l. During concomitant application of A+Reg BG values were considerably and significantly less enhanced (4.02 ± 0.14 mmol/l to 4.89 ± 0.33 mmol/l). During A-infusion, values in percent of controls (Fig. 1) were always significantly different from those during A+Reg-infusion.

2. Plasma immunoreactive insulin
The absolute plasma immunoreactive insulin (IRI) values during A-alone as well as during A+Reg-infusion did not show any significant differences, inspite of the significantly enhanced BG levels during A-treatment. Nevertheless, there are two facts pointing to a rather intact BG-IRI relation during beta-adrenergic action: firstly, one gets a much better correlation of BG with IRI levels during A+Reg-treatment (correlation coefficient 0.766, P < 0.05) than during A-treatment alone (correlation coefficient –0.287, NS), and secondly, IRI values in percent of controls show a slight, but clearly discernable difference (Fig. 2).

3. BG/IRI ratio
Although absolute as well as relative mean values during A-infusion mostly were considerably higher than during A+Reg-treatment, the significance is low owing to high standard deviations (Fig. 3).

4. Cortisol (Fig. 4)
Since the probands knew that they could expect a slight trauma at catheterization, their initial cortisol levels were in the upper normal range during both types of experiments. In both types of experiments, cortisol also uniformly and steadily declined to low normal values, so no differences between the experiments and no persistent influence of catecholaminergic action on this system could be seen.

5. C-peptide (Fig. 5)
Regardless of hyper- or normoglycemia, C-peptide values were hardly distinguishable. Nevertheless, also here there is a highly significant correlation (correlation coefficient 0.8785, P < 0.01) between C-peptide and IRI during A+Reg-treatment, whereas during A-treatment alone (correla-
tion coefficient –0.5641, NS) there is no correlation. Analysis of variance proves that the two regression lines have significantly different slopes ($P = 0.01119$).

Discussion

In spite of the well-known alpha and beta adrenergic influence on the CRH-ACTH-cortisol axis (Shimizu 1984; Porta et al. 1987), no direct catecholaminergic influence on cortisol seems to exist throughout the infusion time. We think that the comparatively low catecholamine concentrations do not disturb the tendency to an inverse BG/cortisol ratio. The differences in the enhancement of BG levels during A- and A+Reg-treatment, however, are striking. Treatment with A increases BG levels considerably, and whole plasma IRI is rather stable and seems not to be able to rise according to the increased BG concentration. This 'rigidity of secretion' (Labhart 1978) is typical for A-action. The beginning of an A-infusion depresses C-peptide concentrations to a lower level, where they remain for the rest of the experiment. These low levels underline the inhibition of IRI secretion.

The BG/IRI ratio rose in a manner similar to BG, emphasizing by its large SEM values that BG and not IRI is the dominating factor in its rising.

![Figure 1](image-url)

**Fig. 1.** Blood glucose values before and during the infusion of 1.2 µg · min⁻¹ · (m²)⁻¹ adrenaline alone (white columns) starting at time 0 min or 1.2 µg · min⁻¹ · (m²)⁻¹ adrenaline together with 120 µg · min⁻¹ · (m²)⁻¹ Regitine (dashed columns) starting at time –30 min. At time –30 min, blood was sampled for control blood glucose determination and a Regitine bolus of 25 mg · (m²)⁻¹ was infused. 1–5 = times of blood check. Abscissa: time (min), ordinate: percent of control blood glucose value at time –30. Mean values ± SEM of 9 experiments.
Concomitant alpha block led to clearly lower BG levels in spite of still enhanced plasma A (0.8 ± 0.15 µg/l at (1), (2) to (5): 1.1–1.4 ± 0.2 µg/l). If higher A and Reg doses are used, as we did in rats with controlled release systems (Porta et al. 1984), sharply increased A-levels are observed.

The considerably lower A and Reg doses used in the present experiments in humans did not lead to any clearly discernible beta adrenergic increase in insulin secretion. Nevertheless, the good IRI-BG as well as IRI-C-peptide correlations show that IRI, in contrast to its behaviour during A-infusion alone, is well able to react upon even slight BG alterations.

### Table 2.

Parametric data of blood glucose (BG), plasma insulin (IRI), BG/IRI ratio and serum C-peptide values after 60 min of infusion with 1.2 µg · min⁻¹ · (m²)⁻¹ of adrenaline (A) alone or together with 120 µg · min⁻¹ · (m²)⁻¹ of Regitine (REG). Mean values ± SEM of 9 experiments.

<table>
<thead>
<tr>
<th></th>
<th>A-infusion</th>
<th>A + REG-infusion</th>
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<tbody>
<tr>
<td>BG (mmol/l)</td>
<td>7.2 ± 0.63</td>
<td>4.7 ± 0.29</td>
</tr>
<tr>
<td>IRI (mU/l)</td>
<td>8.2 ± 0.6</td>
<td>9.0 ± 0.8</td>
</tr>
<tr>
<td>BG/IRI</td>
<td>0.87 ± 0.13</td>
<td>0.52 ± 0.06</td>
</tr>
<tr>
<td>C-peptide (µg/l)</td>
<td>2.4 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
</tbody>
</table>

**Fig. 2.**

Plasma insulin values before and during the infusion of 1.2 µg · min⁻¹ · (m²)⁻¹ adrenaline alone (white columns) starting at time 0 min or of 1.2 µg · min⁻¹ · (m²)⁻¹ adrenaline together with 120 µg · min⁻¹ · (m²)⁻¹ Regitine (dashed columns) starting at time –30 min. At time –30 min, blood was sampled for control plasma insulin determination and a Regitine bolus of 25 mg · (m²)⁻¹ was infused. 1–5 = times of blood check. Abscissa: time (min), ordinate: percent of control plasma insulin value at time –30. Mean values ± SEM of 9 experiments.
On the other hand, even when considering the much more distinguishable percentual increases they seem not by far high enough to bring about the striking differences in BG between the two experiments. Therefore there must be a second and more important mechanism responsible for the fall in BG during A+Reg-treatment. In other words, the success of the experiment, namely creation of normoglycaemia during hyperadrenalinemia, by the use of alpha blockers is not so much due to beta or beta-adrenergic action in the pancreas, as to blocking of the alpha adrenergic glycogenolytic action in the liver.

In male rats, an almost exclusive dependency of adrenergic glycogenolysis on alpha receptors has been shown (Studer & Borle 1982). More recent publications by Hoffman et al. (1981a,b), and nowadays even student's textbooks (Silbernagl & Despopopoulos 1984), maintain that also in humans the A-induced glycogenolytic action in the liver is mainly attributed to alpha (probably alpha 2) receptors. This would then constitute an action of Reg independent of IRI, to push hyperglycaemia towards normal levels during stress.

Contrary to the Reg-actions mentioned above altogether leading to a lowering of BG, its result-

![Fig. 3](image-url)

**Fig. 3.**

Plasma blood glucose/plasma insulin before and during the infusion of 1.2 μg · min⁻¹ · (m²)⁻¹ adrenaline alone (white columns) starting at time 0 min or 1.2 μg · min⁻¹ · (m²)⁻¹ adrenaline together with 120 μg · min⁻¹ · (m²)⁻¹ Regitine (dashed columns) starting at time -30 min. At time -30 min, blood was sampled for control blood glucose and plasma insulin determination and a Regitine bolus of 25 mg · (m²)⁻¹ was infused. 1–5 = times of blood check. Abscissa: time (min), ordinate: per cent of control blood glucose/plasma insulin ratio at time -30. Mean values ± SEM of 9 experiments.
ing beta-adrenergic effect in the periphery is well known to inhibit BG and IRI utilization, which is clearly against our intentions.

Either owing to the short time or to the low doses in our experiment there is no such action, since the ratio IRI/C-peptide does not change anywhere in the two experiments.

However, in real life, the effects of longer alpha blockade (even up to 2 or 3 days before surgery) may well be improved by diminishing the IRI condition of such big muscle masses as those of the legs by recommending some walking exercise.

We are well aware of the fact that alpha blocker application cannot be a long-term solution in the treatment of diabetics owing to their obvious action on circulation and their increasing effect on the numbers of alpha receptors. But for compensation of a stress to be expected, e.g. before examinations or surgery, their possible use may be well worth further investigation.

Acknowledgments

We are indebted to NOVO Industri Å and Ciba-Geigy not only for the supply of drugs, but also for generous financial support.

Fig. 4.
Cortisol plasma values before and during the infusion of 1.2 μg·min⁻¹·(m²)⁻¹ adrenaline alone (white columns) starting at time 0 min or 1.2 μg·min⁻¹·(m²)⁻¹ adrenaline together with 120 μg·min⁻¹·(m²)⁻¹ Regitine (dashed columns) starting at time −30 min. At time −30 min, blood was sampled for control plasma cortisol determination and a Regitine bolus of 25 mg·(m²)⁻¹ was infused. 1–5 = times of blood check. Abscissa: time (min), ordinate: percent of control plasma cortisol at time −30. Mean values ± SEM of 9 experiments.
C-peptide serum values before and during the infusion of 1.2 µg · min⁻¹ · (m²)⁻¹ adrenaline alone (white columns) starting at time 0 min or 1.2 µg · min⁻¹ · (m²)⁻¹ adrenaline together with 120 µg · min⁻¹ · (m²)⁻¹ Regitine (dashed columns) starting at time −30 min. At time −30 min, blood was sampled for control serum C-peptide determination and a Regitine bolus of 25 mg · (m²)⁻¹ was infused. 1−5 = times of blood check. Abscissa: time (min), ordinate: percent of control serum C-peptide at time −30. Mean values ± SEM of 9 experiments.

**Fig. 5.**

References


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Dr Sepp Porta,
Institut für funktionelle Pathologie,
Universität Graz,
 Mozartgasse 1412,
 A-8010 Graz, Austria.