HEMODYNAMIC ALTERATIONS IN INSULIN-INDUCED HYPOGLYCEMIA

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ABSTRACT

Hypotention during insulin-induced hypoglycemia has previously been shown in Inactin-anesthetized rats. The reduction of arterial blood pressure was well correlated with the reduction of plasma glucose. The present study was to explore the possible attributions of certain plasma electrolytes, osmolality, blood volume, hypotensive hormones (including β-endorphin, epinephrine, histamine, insulin, and prostaglandins), baroreflex sensitivity, and vascular tissue responsiveness to angiotensin II (AII), and norepinephrine (NE) in the development of this hypoglycemic-hypotension.

Thirty minutes after insulin injection, plasma calcium increased (from 9.6 ± 0.2 mg% to 10.2 ± 0.2 mg%, $P < 0.05$), whereas plasma potassium decreased (from 4.5 ± 0.1 mEq/L to 3.4 ± 0.2 mEq/L, $P < 0.001$), and both were well correlated with the reduction of plasma glucose. Plasma sodium and osmolality did not significantly change throughout the study. However, normokalemic potassium clamp during insulin hypoglycemia also induced a normal plasma calcium, while hypotension was still evident, indicating that the changes in plasma calcium and potassium during hypoglycemia were the consequence rather than the cause of hypotension. The plasma and blood volumes were also significantly reduced at 30 min after insulin administration (15.2% and 11.8%, respectively; $P < 0.001$) while hematocrit

was increased (45.4 ± 0.6% to 49.0 ± 0.5%, $P < 0.001$). Since hypotension was accompanied with a marked rise in pulse pressure, hypovolemia would be a consequence of vascular dilation, rather than the cause of hypotension.

Insulin injection followed by euglycemic glucose clamp caused no change in arterial blood pressure and heart rate , suggesting that the hypotension observed was a consequence of hypoglycemia rather than the direct action of insulin. The possible releases of hypotensive hormones during hypoglycemia were also tested by blocking the release of epinephrine (bilateral adrenalectomy), β-endorphin blockade (naloxone), or prostaglandins plus histamine blockade (indomethacin, cimetidine plus chlorpheniramine). The results did not show any different hemodynamic responses from those found in the rats subjected to insulin hypoglycemia alone.

The possible involvement of changes in baroreflex sensitivity, and vascular tissue responsiveness to AII and NE during hypoglycemia were also explored. The pressor response to AII (1 μg/kg, i.v.) and the baroreflex sensitivity (BR-NP) which preventing the fall of blood pressure (determined by sodium nitroprusside infusion) was markedly reduced during insulin hypoglycemia. In contrast, the pressor response to NE (6 μg/kg, i.v.) did not change at 30 min after insulin but slowly increased after 60 min, the latter change was correlated with the reduction of baroreflex sensitivity (BR-AII) which normally prevents the rise of blood pressure (determined by AII infusion). The slow increase in pressor response to NE was probably due to the reduced counteraction of BR-AII to the vasoconstrictor effect of NE. The observed reduction in pressor response to AII might be due to the reduced vascular responsiveness to AII *per se*, and together with the reduction of BR-NP, could attribute to the decreased TPR and the postural hypotension commonly observed following insulin injection.

The change in vascular responsiveness to AII was not due to the disturbance of plasma electrolytes because such response was still observed in rats receiving insulin in the presence of normokalemic potassium clamp, during which plasma calcium, potassium, and sodium were maintained at the control level. In contrast, insulin injection with euglycemic glucose clamp abolished the alterations of pressor responses to AII and BR-NP observed after insulin injection. This indicated that such abnormalities were the direct and/or indirect actions of hypoglycemia rather than the direct effect of insulin or electrolyte disturbances. Thus, it was hypothesized that the initial (first 30 min) hypotension observed after insulin injection was due to the simultaneous reductions in vascular response to endogenous AII and BR-NP. The results also showed a gradual return to normal of pressor response to AII in spite of the presence of hypoglycemia and it was explained that the vascular response to AII was probably still reduced but the apparent recovery was because of the concurrent decrease of BR-AII during this period. Prolonged hypotension was thus still observed by the still reduced pressor response to AII. The baroreflex (BR-NP) during this period also show sign of recovery and it should reflexly restore the blood pressure. However, this baroreflex (BR-NP) which should be activated by hypotension was not fully responsive because the body has changed its "set point" to accept or tolerate a lower blood pressure level.