Review Articles

Catecholamines and Diabetes Mellitus

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The sympathetic nervous system is of major importance in the regulation of several physiological functions, such as cardiovascular and metabolic homeostasis. The last decade has seen an increasing interest in catecholamines as transmitters in the central nervous system and as regulators of endocrine secretion. There have been considerable advances in the understanding of the biochemistry of catecholamines [7, 56].

The potential role of catecholamines in a number of human diseases has however, until recent years been studied to a limited extent due to lack of methods for measurement of sympathetic nervous activity (SNA). Much work has been done to develop a radioimmunoassay for determining the enzyme dopamine-beta-hydroxylase in serum, which unfortunately has turned out to be a poor index of SNA [90]. The development of enzymatic isotope-derivative techniques [53, 54] enabled reliable measurements of plasma noradrenaline (NA) and adrenaline (A). Studies in man have shown that plasma NA is an index of SNA [34, 41].

The present survey deals mostly with the function of the sympathetic nervous system in various clinical situations occurring in diabetic patients, particularly

with plasma and tissue concentrations of noradrenaline and adrenaline.

Catecholamines in Patients with Untreated Diabetes Mellitus

The metabolic changes observed in untreated diabetics are, in many respects, similar to those produced by infusion of catecholamines and include hyperglycaemia, decreased glucose tolerance, elevated free fatty acids and ketone bodies in plasma and a reduced insulin response to glucose.

There are important questions concerning a) the possible significance of the catecholamines in the development of ketoacidosis and b) whether the catecholamines may be responsible for the abnormally low insulin response to glucose which is observed in most patients with diabetes mellitus.

A number of studies indicate that emotional factors may aggravate the metabolic state in patients with diabetes mellitus [82, 83, 107, 141]. Stress, myocardial infarction and burns, for example, are known to induce a diabetes-like change in metabolism that will be discussed later.

In a number of studies, Carlström [21, 22] has shown that exercise induced greater lipid mobilisation in untreated juvenile diabetics in comparison with normal subjects. Concentrations of plasma free fatty acids were normalised after insulin treatment, while plasma glycerol was nearly normalised. Hansen [72, 73] has shown that there was a greater rise in growth hormone during exercise in untreated juvenile diabetics which was nearly normalised after insulin treatment. Both the exercise induced lipid mobilisation and the rise in plasma growth hormone during exercise are probably mediated through the sympathetic nervous system.

Abbreviations: NA = noradrenaline; A = adrenaline; SNA = sympathetic nervous activity

Fig. 1. Plasma catecholamines in subjects at rest, during, and after exercise in the supine position. Left: two diabetics, ○—○—○ untreated, ●—●—● treated. Right: average values of five controls $\pm$ SD. (Reproduced with permission from: Scand. J. Clin. Lab. Invest. [25])

Fig. 2. Correlation obtained in ten diabetics between plasma noradrenaline and total carbon dioxide in plasma. (Reproduced with permission from: Diabetes [32])

Porte [119] has presented some experiments suggesting that the adrenergic response to dehydration in diabetics may aggravate their metabolic status, while Havel [76] has suggested that autonomic neuropathy in diabetics may protect them from the development of keto-acidosis.

Baker, Kaye & Haque [9] observed an increase in ketone body responsiveness to adrenaline infusions in diabetic children while the rises in glucose and free fatty acids were comparable to those obtained in normal children. Gerich et al. [67] and Benson et al. [14] reported that the glucagon response to adrenaline infusion was greater in juvenile diabetics than in normal subjects.

Plasma catecholamine concentration is elevated in untreated diabetics [25]. Figure 1 shows the total

plasma catecholamine concentration (the sum of NA and A, but mainly NA) in two juvenile diabetics studied at rest and during exercise. During ketosis the diabetics demonstrated elevated resting values and the peak plasma concentration in response to exercise was approximately eight times higher than in the controls. The pulse rate was also higher in the untreated diabetics than in the controls. After treatment with insulin, the catecholamine values at rest and during exercise were similar to those obtained in the controls.

In a later study [32] plasma NA and plasma A were measured in 10 diabetics hospitalised in keto-acidosis and again after treatment with insulin. All the untreated diabetics had plasma NA values exceeding the upper 95 per cent limit of the values obtained in the controls. The large variation among individual patients, 0.36 ng/ml to 4.19 ng/ml, could be explained by the different degrees of metabolic derangement upon hospitalisation. Plasma NA was correlated to the total carbon dioxide in plasma (Figure 2), to the pulse rate and to the blood glucose concentration. Plasma adrenaline was elevated in 4 of the 10 patients. After treatment with insulin, plasma NA and A concentrations were similar to those obtained in the controls.

Studies in diabetic patients after withdrawal of insulin [4] showed that plasma NA and A were normal in the early stage after withdrawal of treatment. It is uncertain, of course, to what extent such experiments mimic patients developing keto-acidosis outside the hospital. In a significant number of patients with keto-acidosis, omission of the insulin is the causal factor. Elevated catecholamines probably constitute an important compensation to volume depletion and disturbed cell function, thus maintaining vital body functions at the expense of an aggravated metabolic disturbance. Schade & Eaton [132] have recently emphasised the role of anti-insulin hormones in the development of keto-acidosis.

It is mentioned above that the metabolic changes observed in diabetes mellitus are similar to those produced by infusion of catecholamines. Glucose-stimulated insulin secretion is reduced under both conditions. It must be emphasised, however, that basal insulin secretion differs in these two conditions. While juvenile diabetic patients have normal or reduced insulin values in comparison with control subjects, basal insulin secretion is elevated during prolonged infusions of catecholamines and in patients with myocardial infarction [39, 125].

There is some evidence indicating that the defective insulin secretion in diabetics is not caused by the catecholamines; insulin secretion in response to isoproterenol (a beta-adrenergic receptor agonist) was

Table 1. Acute effects of insulin on the cardiovascular system

Parameter	Change	Mechanism	Comments
Heart rate	Increases	Non-adrenergic	
Arterial blood pressure	Unchanged or decreases	?	Decreases in patients with neuropathy
Plasma noradrenaline	Increases	Compensatory to hypovolaemia or antagonising effects of insulin on some actions of NA?	Plasma adrenaline is unchanged
Forearm blood flow	Decreases	?	
Plasma volume	Decreases	?	
Haematocrit	Increases	?	Changes smaller than in plasma volume
Urinary albumin excretion	Increases	Glomerular	Beta-2-microglobulin excretion decreases
Glomerular filtration rate and renal plasma flow	Decreases	?	Due to the fall in blood glucose concentration?
Micropinocytotic vesicles in capillary endothelial cells	Increases	?	Free vesicles

often preserved in diabetics in whom glucose had no effect [45, 126]. This provides evidence not only that the glucose receptor is distinct from the beta-adrenergic receptor, but also indicates that the beta-adrenergic receptor, is unlikely to be responsible for the defective insulin secretion to glucose in diabetes mellitus. Linde & Deckert [96] observed that administration of phentolamine during an intravenous glucose tolerance test increased glucose-stimulated insulin secretion to about the same extent in diabetics and in controls. Robertson et al. [124] have reported that diabetics have a greater increase in basal and glucose-stimulated insulin secretion after alpha-adrenergic receptor blockade with phentolamine. Total plasma catecholamine concentration was also found to be higher in 5 diabetics as compared to 12 normal subjects. It is our experience, however, that plasma NA and A concentrations are normal in patients with short term-diabetes without signs of diabetic neuropathy, provided that the metabolic status is reasonably well controlled [25, 32]. It must be added, however, that IV injection of insulin results in an increased SNA and a rise in plasma NA (see below).

Very recently Cryer et al. [42] reported a study of plasma NA and A in 100 non-ketotic diabetics. Eleven patients had increased standing plasma NA concentrations unrelated to insulin administration. Seven of these had elevated supine plasma NA levels. Three of the 11 patients exhibited postural hypotension (hyperadrenergic postural hypotension) (see below).

Recapitulating, a number of studies have demonstrated that SNA is increased in poorly controlled diabetics, and while elevated plasma catecholamines

may aggravate the metabolic status they are probably important in the maintenance of vital body functions in the more seriously ill patients. On the other hand, it seems unlikely that catecholamines are responsible for the defective insulin response to glucose which is observed in most patients with diabetes mellitus.

Acute Cardiovascular Effects of Insulin

It is now known that insulin apart from its effects on metabolism and on ion fluxes has a marked acute effect on SNA and the cardiovascular system (Table 1).

Intravenous injection of insulin increases plasma NA [32, 35, 70] and heart rate [70, 114] and decreases peripheral blood flow [70]. However, despite the increase in plasma NA and heart rate after IV insulin, arterial blood pressure remains unchanged in subjects with an intact autonomic nervous system and may even decrease in patients with autonomic neuropathy [61, 102, 103, 115]. Furthermore, we have found that insulin induces hypovolaemia and increases urinary excretion rate of albumin and the number of micropinocytotic vesicles in muscle capillary endothelial cells [70, 104, 113].

The cardiovascular effects of insulin are not due to hypoglycaemia, since they occur even when the blood glucose concentration does not decline below normal fasting values. In addition, the patients examined did not have symptoms of hypoglycaemia and plasma A did not increase [70].

The decrease in plasma volume after IV insulin could be apparent rather than real because of venous pooling. This is unlikely to be the sole explanation

because there are parallel, although smaller changes in peripheral haematocrit [101] and IV injection of insulin is associated with an increased transcapillary escape rate of albumin (see below).

The mechanism of hypovolaemia induced by insulin has not been fully established. No correlations have been found between changes in blood glucose and haemodynamic changes observed after insulin [70, 104]. A decrease in blood glucose (e.g. of 100 mg/100 ml) after insulin is followed by a decrease in plasma volume secondary to the intracellular transfer of glucose and the ensuing decrease in plasma osmolality. However, calculations based on simple assumptions [86] show that the decrease in plasma volume after insulin is at least 5 times larger than could be expected from changes in plasma osmolality. Furthermore, this mechanism cannot explain the concomitant decrease in the intravascular pool of albumin.

The passage of large molecules across the endothelial cell probably takes place by vesicular transport [151]. It has recently been shown that insulin increases the number as well as the ratio between free and attached micropinocytotic vesicles in endothelial cells in muscle capillaries in diabetic rats [113]. Although the relationship between the effect of insulin on cardiovascular function [70] and on endothelial micropinocytotic vesicles needs further clarification the present results do suggest that adequate concentrations of insulin may be required for the normal function of endothelial cells.

The acute effects of insulin on renal haemodynamics and protein excretion have recently been studied in detail in juvenile diabetics [104]. Insulin decreased blood glucose concentration (from 250 mg/100 ml to 117 mg/100 ml), glomerular filtration rate (9%), renal plasma flow (13%), urine output, renal excretion rates of several electrolytes (sodium, potassium, phosphate), and increased pulse rate (from 66 to a maximal value of 75 beats/min) during the first 90 min after injection. Blood pressure and filtration fraction remained unchanged.

Insulin increased urinary excretion of albumin [104]. This effect was most probably due to increased filtered amounts of albumin after insulin, because urinary excretion rate of beta-2-microglobulin decreased, suggesting that tubular reabsorption of protein was increased after insulin. Furthermore, there was no correlation between changes in urinary albumin and beta-2-microglobulin excretion.

The increased urinary excretion of albumin after insulin is not due to the fall in blood glucose concentration. IV injection of insulin resulted in increased excretion rates of albumin in diabetics in whom blood glucose concentration was maintained at an unchanged level by glucose infusion. The fall in

glomerular filtration rate and renal blood flow may, however, be due to the fall in blood glucose. (Unpublished experiments: Mogensen, Christensen & Gundersen).

The mechanism of action of insulin on the cardiovascular system is not known, but it has been assumed that hypovolaemia induced by insulin is counterbalanced by an increased SNA, maintaining arterial blood pressure at normal levels at the expense of an increase in heart rate and a decrease in peripheral blood flow [70]. Recent studies in rabbits have, however, shown that the stimulatory effect of insulin on heart rate is not mediated by the autonomic nervous system [85]. Therefore the rise in plasma NA after insulin may reflect a compensatory increase in SNA secondary to antagonising effects of insulin on some actions of NA in the same way as adrenergic receptor blockade leads to a compensatory rise in SNA and in plasma NA [37, 62, 63, 75]. It is well-known that insulin antagonises metabolic effects of NA and a similar interaction has been observed within the cardiovascular system [94].

It should be emphasised however, that IV insulin results in peripheral vasoconstriction [70] and further studies are required before the mechanisms of insulin actions on the cardiovascular system are fully understood.

Interestingly, effects of insulin on SNA and the cardiovascular system are also observed in normal subjects after an oral glucose load which increases serum insulin. Heart rate increased in a group of normal subjects from 30 min after an oral glucose load to a maximum value at 120 to 150 min. In a group of insulin requiring diabetics there was no change in heart rate after oral glucose apart from an early and short-lived response [77]. In the same study it was also found that 3 normal subjects showed a pronounced but shortlived increase in urinary excretion of albumin at 30 to 60 minutes after the oral glucose.

Arterial hypotension after oral glucose has been reported in a non-diabetic patient with severe Parkinsonism [133].

It has recently been shown in animal experiments that feeding increases turnover of NA in the heart [91].

In summary, insulin and glucose result in an increased release of NA. It is possible that net effects of NA are reduced after insulin. The mechanisms of actions of insulin on SNA and the cardiovascular system are not fully understood.

Catecholamines in Long-term Diabetics

Diabetic neuropathy includes sensory and motor neuropathy, autonomic neuropathy and encephalopathy. Autonomic neuropathy may lead to im-

tence, bladder dysfunction, gastrointestinal disturbances and occasionally to orthostatic hypotension. It develops in the same way as diabetic angiopathy, in the course of a number of years, and is most pronounced in those who have had diabetes from 10 to 25 years. Diabetic neuropathy is most pronounced in the lower extremities, but can be demonstrated in all parts of the body. The extensive literature dealing with diabetic neuropathy will not be reviewed here [28, 48, 49, 99].

Many different autonomic nervous system abnormalities have been described in diabetics: variability in resting blood flow in feet [24], heart rate [71, 148], and pupil area [69] is considerably reduced in diabetics compared to controls due to autonomic neuropathy. Functions such as blood pressure and body temperature, which are normally kept within a narrow range during changing conditions, fluctuate more in diabetics [1, 27].

The consequences of diabetic autonomic neuropathy have, unfortunately, been subject to only a few studies. Ewing et al. [58] reported that mortality was higher in a group of diabetics with autonomic neuropathy when compared to a group of patients without autonomic nervous system abnormalities.

It has recently been shown that cardiovascular responses to physical exercise are impaired in diabetic autonomic neuropathy [80]. Resting heart rate was higher and the increase in heart rate at a low work load was diminished in patients with autonomic neuropathy compared to control patients, suggesting a vagal defect. Maximal heart rate, maximal systolic blood pressure, maximal oxygen uptake and the greatest tolerable work load were reduced in patients with neuropathy. The relationship between heart rate and relative work load and between systolic blood pressure and relative work load in patients with autonomic neuropathy, suggested impaired SNA.

Long-term diabetics are supersensitive to IV infusion of catecholamines [11, 105]. This supersensitivity is probably caused by several different mechanisms. First, axonal-uptake, a function which is important for the biological inactivation of the catecholamines, decreases when adrenergic nerves degenerate, and the concentration of the amines at receptor sites increases. Secondly, the chronic absence of the neurotransmitter probably increases the sensitivity by changing the availability of receptors [46, 79, 140, 142, 149]. Thirdly, lack of blood pressure-restraining reflexes due to autonomic neuropathy may also be of importance.

Plasma catecholamine concentration (mainly NA) is reduced in both the supine position and when standing in long-term diabetics with signs of somatic neuropathy. There is a close correlation between plasma catecholamine concentration and the vibra-

Fig. 3. Correlation obtained in long-term diabetics with and without neuropathy between plasma catecholamine concentration (mainly noradrenaline) when standing up (log scale) and vibratory perception threshold in the feet. (Reproduced with permission from: J. Clin. Invest. [27])

Fig. 4. Increase in plasma catecholamine concentration (mainly noradrenaline) and rise in heart rate after 5 min in the standing position. The regression lines are also plotted on the figure. Upper curve (○): normal subjects. Lower curve (●): long-term diabetics with neuropathy. (Reproduced with permission from: J. Clin. Invest. [27])

tory perception threshold in the feet in long-term diabetics [27] (Figure 3). The vibratory perception threshold in the feet has previously been shown to be correlated to the degree of autonomic neuropathy in diabetics as indicated by lack of spontaneous variability in resting blood flow in the feet [24].

Diabetic patients with an abnormal fall in arterial blood pressure when standing often show a normal or an exaggerated rise in pulse rate [28]. The abnormally low response in plasma catecholamines in long-term diabetics when standing is due to a selective decrease in plasma NA "ordinate" components (Figure 4) while the pulse rate related plasma NA component and rise in pulse rate on standing are normal [27].

The tissue concentrations of NA, which reflect the density of sympathetic innervation were found to be considerably reduced in specimens of both arteries and hearts obtained from long-term diabetics at post-mortem [109]. The mean NA concentration ranged

Fig. 5. Noradrenaline (ng/gm of tissue) in the radial artery, the posterior tibial artery, and the femoral artery of six control subjects and of six diabetic patients. Results are mean values $\pm$ SEM. (Reproduced with permission from: Diabetes [109])

between 6 to 20% of the corresponding mean values in the controls (Figure 5). The pronounced reduction in the NA concentration in the heart of diabetics was also found in patients who had died without heart failure.

The depletion of the NA stores in the heart indicates that an important supportive mechanism is lost in long-term diabetic patients. This is probably of importance in stress, especially after acute myocardial infarction, where a high SNA is necessary for the maintenance of an adequate myocardial performance and the cardiac denervation may contribute to the higher mortality observed in diabetic patients.

Cryer et al. [42] studied plasma NA and A in 100 non-ketotic diabetics. Seven patients had postural hypotension and blunted plasma NA responses to standing. Eleven patients had increased standing plasma NA concentrations. Seven of these patients also had elevated supine plasma NA levels. Three of the eleven patients exhibited postural hypotension (hyperadrenergic postural hypotension). One such patient was also present in our own study (case 22) [27]. Orthostatic hypotension in this patient was classified as arterial orthostatic anaemia [16], which is associated with a hyperadrenergic response [146] and the abnormal reaction was not considered related to diabetes mellitus. One of the normal subjects showed a similar response. The elevated plasma NA and hyperadrenergic postural hypotension in some

patients with diabetes mellitus is not due to vascular resistance to NA but related to a reduced red cell mass (P. E. Cryer: Personal Communication).

Catecholamines in Hypophysectomised Diabetics

Long-term diabetics hypophysectomised for treatment of diabetic retinopathy on replacement therapy with corticosteroids and thyroid hormones show, despite a severe degree of neuropathy, a prompt rise in plasma catecholamine concentration (mainly NA) in response to standing [27]. Basal plasma catecholamine concentration is also elevated in comparison to the non-operated patients. It is the pulse rate related plasma NA component which is increased in the hypophysectomised diabetics, while the "ordinate" component is just as abnormally low as in the non-operated long-term diabetics with neuropathy [27]. Thus there is no evidence that the neuropathy has disappeared after hypophysectomy and the vibratory perception threshold is still very abnormal. Other authors have reported elevated urine excretion of NA after hypophysectomy [106]. In contrast to the findings in the non-operated diabetics with neuropathy the hypophysectomised patients showed a positive correlation between rise in plasma NA when standing and fall in arterial blood pressure [27]. This suggests that the elevated plasma NA concentration after hypophysectomy was a compensatory phenomenon, caused perhaps by a decreased basal metabolic rate, low cardiac output, and reduced red cell mass.

The haemodynamic changes which occur in hypophysectomised diabetics treated with cortisone and thyroid hormones are in many respects, similar to those observed in patients with myxedema. Patients with myxedema also demonstrate an elevated plasma NA concentration and an increased SNA [29, 31, 90]. It is possible that growth hormone like thyroid hormones [95] has a direct stimulatory effect on cardiac muscle. We have the impression that hypophysectomised diabetics over the course of some years, develop heart failure more often than the non-operated patients.

Hypophysectomy slows the progression of diabetic retinopathy and of visual impairment [100, 110]. Hypophysectomy will also increase skin capillary resistance in diabetics, often to values above those observed in normal subjects [23, 38]. Vasoconstriction and the elevated plasma NA concentration may be one of the mechanisms by which hypophysectomy normalises capillary resistance [27, 28, 38]. Many studies have shown that skin capillary resistance is closely correlated to blood flow in skin [30,

128, 139]. Retinal blood flow in diabetics has also been reported to decrease after hypophysectomy [87].

The degree of hyperglycaemia in diabetics is not much influenced by hypophysectomy but ketonaemia is likely to be reduced. We have previously demonstrated a relationship between blood flow in the forearm and the degree of ketoacidosis [26]. It is therefore possible, although unlikely, that effects of hypophysectomy on capillary fragility are mediated by a decrease in blood ketone body concentration.

Urinary excretion of A during insulin induced hypoglycaemia is reduced in hypophysectomised diabetics [98]. This is due to the fact that the formation of A in the adrenal medulla depends on a high glucocorticoid concentration in the sinusoidal blood which reaches it from the adrenal cortex [117]. The glucocorticoid concentration in the adrenal medulla decreases after the abolition of ACTH secretion because the cortisone or hydrocortisone used for replacement therapy are diluted in the systemic circulation before they reach the adrenal medulla.

Catecholamine Induced Diabetes

Role of Catecholamines in the Regulation of Insulin Secretion

Intravenous infusion of A and NA in man as well as stimulation of the sympathetic nerves to the dog pancreas has been shown to inhibit glucose stimulated insulin secretion [120, 121, 122]. Human pancreatic beta cells have both alpha- and beta-adrenergic receptors, which are inhibitory and stimulatory, respectively [118]. The intravenous infusion of A to overnight-fasted man is followed by a small decrease in fasting insulin, thereafter insulin concentration increases accompanying the rise in blood glucose and free fatty acid concentrations. Glucose stimulated insulin secretion is however, greatly attenuated [125]. Inhibition of insulin secretion is not primarily responsible for the mobilisation of fuels but free fatty acids and blood glucose cannot be elevated at the same time without relative inhibition of insulin secretion. This is due to the fact that lipolysis is exceedingly sensitive to glucose induced insulin secretion.

There are divergent opinions as to whether the sympathetic nervous system and plasma A may be of importance in the physiological regulation of insulin secretion during resting conditions. Studies employing alpha- and beta-adrenergic receptor blocking agents have given inconsistent results. Basal and glucose stimulated insulin secretion have been found to increase and decrease after alpha- and beta-adrener-

gic receptor blocking agents, respectively. In many studies however, no effects were found.

Basal and glucose stimulated insulin secretion were found to be normal in patients with transection of the cervical spinal cord in whom SNA is considerably reduced. Similar negative results have been observed in adrenalectomised patients [18]. The net effect of catecholamines on insulin secretion is inhibitory and the results suggest that SNA is of no importance in the regulation of basal and glucose stimulated insulin secretion in the resting state.

Standing was found to have no effect on glucose-stimulated insulin secretion despite a moderate increase in SNA [36].

Fasting insulin decreases during exercise [62, 63, 64, 65, 84, 143]. Glucose uptake is increased in exercising muscles by an insulin independent mechanism and during exercise there is a need for mobilisation of fuels from peripheral tissues as well as for increased glycogenolysis. A decrease in insulin secretion is therefore appropriate. The evidence indicates that suppression of insulin secretion during exercise is at least partly due to an increased SNA and elevated plasma A concentrations [63].

An increased SNA and elevated plasma A concentrations are to some extent responsible for the diabetes-like change in metabolism observed in many pathophysiological states. Patients with acute myocardial infarction [5, 39, 43, 89, 93, 111, 129, 138], burns [6, 15], deep hypothermia [12, 13] and patients undergoing surgery [108] show hyperglycaemia, impaired glucose tolerance and elevated free fatty acids. Insulin concentration is elevated but inappropriately low in relation to the blood glucose concentration.

In patients with diabetes mellitus the stress states mentioned above may seriously aggravate metabolic status; infections in particular, are a well known predisposing cause of ketoacidosis [107].

Mechanisms of Catecholamine Induced Diabetes in Patients with Acute Myocardial Infarction

Plasma NA and A are elevated in patients with acute myocardial infarction and in the individual patients the level is fairly constant during the first two days after admission to hospital, being dependent on the degree of illness [39, 150].

After an overnight fast plasma NA showed a strong correlation with blood glucose concentration (Figure 6), but not with plasma free fatty acids or serum insulin in a group of patients with acute myocardial infarction [39]. The lack of a close relationship between plasma NA and free fatty acids may be explained by the fact that the concentration of free

Fig. 6. Correlation between fasting blood glucose concentration in patients with acute myocardial infarction and fasting plasma noradrenaline concentration. $2P < 0.001$. (Reproduced with permission from: J. Clin. Invest. [39])

Fig. 7. Correlation between glucose tolerance in patients with acute myocardial infarction expressed as the K value and plasma noradrenaline concentration during the IV glucose tolerance test. $2P < 0.01$. (Reproduced with permission from: J. Clin. Invest. [39])

Fig. 8. Rate of fall of free fatty acids after IV injection of glucose in patients with acute myocardial infarction expressed as the K value and plotted on the ordinate vs. plasma noradrenaline concentration during the IV glucose tolerance test. $2P < 0.05$. (Reproduced with permission from: J. Clin. Invest. [39])

fatty acids also depends on the basal insulin concentration. A more detailed analysis using multiple regression demonstrated a positive correlation between free fatty acids and NA in plasma, and a negative correlation between free fatty acids and serum insulin. NA and insulin thus produced independent effects on lipolysis. It is not possible therefore, to predict the concentration of free fatty acids in plasma in patients with acute myocardial infarction without knowing both the plasma NA and the serum insulin concentration. It seems likely that NA increased blood glucose concentration which in turn neutralised the inhibitory effect of NA on basal insulin secretion, with the net effect that serum insulin was slightly increased although still inappropriately low in relation to the prevailing blood glucose concentration. NA stimulated lipolysis but the slightly elevated basal insulin secretion inhibited lipolysis with the net effect that free fatty acids were elevated and did not correlate directly with the plasma NA concentration.

The mechanisms of the changes appear to be different after an IV glucose tolerance test. Plasma NA and A concentration did not change after administration of glucose. Glucose tolerance was reduced in most patients with acute myocardial infarction. The glucose K value (fractional disappearance rate) showed a negative correlation with the plasma NA (Figure 7) and a positive correlation with serum insulin. Plasma NA and the rise in serum insulin were also closely correlated. The statistical effects of the two variables on glucose K value could not be separated from each other. The rate of fall in plasma free fatty acids concentrations was correlated with both the rise in serum insulin after glucose and plasma NA (Figure 8). These results would therefore indicate that, during the glucose tolerance test, the effects of NA on the glucose K value and on the rate of fall of free fatty acids in plasma were mediated indirectly via a suppression of insulin secretion.

This difference in plasma NA-insulin relationship in the basal state and during glucose tolerance tests may be explained by the different glucose-insulin interrelationships in the two conditions. As mentioned above, fasting blood glucose concentration showed a strong correlation with plasma NA. During the glucose tolerance test there was no correlation between maximal glucose values obtained and plasma NA, due to the fact that all patients were given identical amounts of glucose so that the inhibitory effects of the various plasma NA levels could be more easily demonstrated.

Plasma cortisol [8, 20, 74, 97, 123] and glucagon [92] have also been reported to be elevated in patients with acute myocardial infarction and correlated with the blood glucose concentration [20, 92]

and presumably with the plasma NA concentration and may thus contribute to the observed alterations in metabolism.

The patients with acute myocardial infarction demonstrated a relative inhibition of insulin secretion, i. e. the relative response rather than the absolute insulin values were reduced. The initial phase of acute myocardial infarction is therefore characterised by an inappropriately low insulin response to glucose and insulin antagonism. Compensated insulin antagonism with elevated basal insulin concentrations and a normal response to glucose may be a mild stress response and therefore a later appearing phenomenon [6, 93].

Catecholamines and Hypoglycaemia

Hypoglycaemia is a well known stimulus for plasma adrenaline secretion. There is a close correlation between the blood glucose concentration attained during hypoglycaemia and rise in plasma A (Figure 9) as well as between rise in plasma A and the subsequent rise in blood glucose concentration. There is also a twofold rise in plasma NA during hypoglycaemia [35, 66]. A fall in blood glucose concentration per se in diabetics results in a rise in plasma NA, but plasma A does not change provided that blood glucose concentration remains above normal fasting levels.

It is important to realise that most studies of hypoglycaemia have involved the use of insulin which decreases both glucose and free fatty acids in plasma. This experimental design may mimic the hypoglycaemia observed in diabetic patients. In the physiological state as well as in a number of pathological situations, hypoglycaemia is accompanied by decreased not increased insulin secretion.

Many different mechanisms may be involved in the restoration of a normal blood glucose. These include: direct hepatic effects of hypoglycaemia, a controversial point [127, 137]; indirect hepatic effects induced by neural or endocrine changes; peripheral or extrahepatic changes which can influence blood glucose either by changes in the utilisation of glucose or by modulating the supply of gluconeogenic substrates to the liver. In experiments where hypoglycaemia was induced by insulin administration as well as in diabetic patients, the rapid disappearance and breakdown of circulating insulin is of importance [112]. Hypoglycaemic inhibition of endogenous insulin secretion may also be of importance.

The possible importance of the sympathetic nervous system and plasma A is emphasised by the finding that administration of 2-deoxy-D-glucose to spi-

Fig. 9. Relation between mean plasma adrenaline at 30 to 45 min during hypoglycaemia and mean blood glucose concentration at 15 to 30 min after IV injection of insulin. (Reproduced with permission from: Eur. J. Clin. Invest. [35])

nal man is not followed by any change in blood glucose, lactate and free fatty acids in contrast to the pronounced changes observed in normal subjects [17]. Studies by the same authors [19] showed that administration of 2-deoxy-D-glucose to adrenalectomised subjects resulted in an attenuated but statistically significant increase in blood glucose which could not be explained by changes in glucagon, growth hormone or cortisol. Lactate and free fatty acids concentrations did not change in the adrenalectomised subjects. This finding indicates that NA may contribute to counterregulatory events after administration of 2-deoxy-D-glucose.

Blood glucose and free fatty acids rebound to normal following hypoglycaemia more slowly after administration of adrenergic antagonists [3, 40, 44, 47, 147]. The effect of propranolol on recovery of glucose after IV insulin is not very pronounced. It should be emphasised, that the hyperglycaemic and hepatic glycogenolytic response to catecholamines is mediated by both alpha- and beta-adrenergic receptors as well as by other yet unclassified receptors [88, 131].

The findings that children with ketotic hypoglycaemia are both exquisitely sensitive to insulin and also have a defective A response to hypoglycaemia [33, 136] serve to emphasise the importance of the sympathetic nervous system and plasma A in re-establishing normoglycaemia.

Table 2. The effects of adrenaline infusion (6 µg/min for 20 min) on plasma adrenaline, blood glucose, serum insulin and blood metabolites in normal subjects. Results are means ± SEM

		Basal	After 20 min infusion	p
Blood glucose	mg/100 ml	71 ±2	98 ±4	<0.001
Serum insulin	µU/ml	11 ±1	9 ±1	NS ^a
Plasma adrenaline	ng/ml	0.02 ±0.01	0.71 ±0.13	<0.01
Plasma noradrenaline	ng/ml	0.18 ±0.04	0.19 ±0.06	NS
Blood lactate	mmol/l	1.02 ±0.12	1.64 ±0.13	<0.01
Blood pyruvate	mmol/l	0.096±0.01	0.102±0.014	NS
Blood alanine	mmol/l	0.30 ±0.02	0.28 ±0.01	NS
Blood glycerol	mmol/l	0.154±0.012	0.266±0.031	<0.05
Blood 3-hydroxybutyrate	mmol/l	0.217±0.046	0.472±0.105	<0.05
Blood acetoacetate	mmol/l	0.074±0.013	0.095±0.009	<0.05

^a significantly reduced at 10 min. Taken from [35]

In contrast to this are reports that adrenalectomised or splanchnectomised patients have no adrenaline responses but normal glucose responses to hypoglycaemia [57, 61, 68]. Blood glucose levels attained in these studies were not very low. However, the most likely explanation of these negative results is that the recovery of blood glucose after IV insulin in man may be influenced by rises in both plasma A and in plasma glucagon. Increase in glucagon secretion during hypoglycaemia is not dependent on the sympathetic nervous system and plasma A [55, 116 144].

Sacca et al. [130] reported that in demedullated reserpine-treated rats, insulin-induced hypoglycaemia was more pronounced than in control rats despite markedly increased plasma glucagon in both groups of rats. In adrenodemedullated rats the exercise-induced decrease in liver and muscle glycogen was found to be abolished [37].

The sympathetic nervous system and plasma A may act through several mechanisms. Splanchnic nerve stimulation and plasma A increase hepatic glucose output and may inhibit insulin secretion from the pancreas [50, 51, 52, 59, 81, 134, 135].

Apart from hepatic effects, adrenaline can mobilise several gluconeogenic substrates [2, 10, 121, 145]. Table 2 shows the results of a study where A was infused IV at a rate of 6 µg/min for 20 min in 4 normal subjects [35]. Mean basal A rose from 0.02 ng/ml to a mean value of 0.71 ng/ml, well within the range of concentrations observed during hypoglycaemia. Plasma NA did not change. There was a rise in blood lactate, glycerol and in ketone body concentrations while pyruvate and alanine did not change. Ketone body concentrations increased partly due to enhanced lipolysis with increased free fatty acids supply to the liver and partly to a direct stimulation of hepatic ketogenesis by A [78]. Both ketone

bodies and free fatty acids provide important alternative fuels for peripheral tissues and will thus conserve glucose. Lactate must originate from glucose, representing recycling rather than real new glucose, but the energy required for glucose formation from lactate will have come from free fatty acid oxidation so there is a gain of glucose energy. During a more prolonged A infusion Weisswange et al. [145] have observed a rise in blood alanine of 0.05 mmol/l, which is small, however, when compared with the other substrates. The failure of alanine to rise, probably reflects the lack of change in pyruvate. The lactate/pyruvate ratio rises sharply, probably as a result of enhanced free fatty acid oxidation which causes an increase in the ratio of NADH to NAD [35].

In addition to the catecholamines the concentrations of other hormones also rise during hypoglycaemia. Glucagon secretion is increased. Plasma cortisol and growth hormone rise in response to hypoglycaemia but do not seem to be of importance for the normalisation of the glucose concentration or for the rebound of free fatty acids [3, 17, 60], although hypophysectomised longterm diabetics are exquisitely sensitive to insulin due to the abolition of growth hormone secretion.

Most of the symptoms which accompany hypoglycaemia are not due to A [61]. Heart rate increases before plasma A increases and the increment is probably mediated by the sympathetic nerves to the heart. The increase in heart rate is transient and heart rate returns to normal levels at the time very high A values are present suggesting increased vagal nerve activity [35]. A normal rise in heart rate during hypoglycaemia has also been noticed in patients who previously had been treated with splanchnectomy and in whom there was no increase in urinary excretion of A during hypoglycaemia. Palpitation was absent however, in the patients and the pulse

pressure did not increase as in normal subjects [61]. In tetraplegics the usual symptoms accompanying insulin hypoglycaemia did not occur. These subjects felt drowsy and lapsed into a light sleep which was reversed by IV glucose [102].

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