Review Articles

Acute Effects of Insulin on Cardiovascular Function and Noradrenaline Uptake and Release

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The purpose of this review is to summarize recent studies of the acute effects of insulin on cardiovascular function and the release and uptake of noradrenaline (NA). This subject is complex because insulin may act through several different mechanisms – e.g. by changes in blood glucose or by increasing the release of catecholamines (Table 1). The present discussion will focus on the interplay between insulin and NA release and on changes that are unrelated to the counter-regulatory response to falling plasma glucose. It is important to distinguish between experiments where hypoglycaemia did or did not develop because, in the former condition, insulin may result in a considerable rise in plasma adrenaline which has pronounced effects on the cardiovascular system. However, it must be emphasized that although the magnitude of the counter-regulatory response to falls in the plasma glucose concentration is inversely related to the absolute plasma glucose concentration there is, especially in diabetic patients, no absolute plasma glucose concentration threshold for activation of glucose counter-regulatory systems [1, 2]. If the blood glucose concentration is maintained at a constant level by glucose infusion after insulin administration, then the observed changes in cardiovascular function or plasma NA concentration cannot be related to glucose counter-regulatory systems.

Direct Effects of Insulin

Several authors have shown in animal studies and in isolated preparations that insulin increases cardiac muscle contraction, an effect which is not dependent on glucose or catecholamines [3–5]. Page et al. [6] showed

that insulin increased heart rate in diabetic patients with normal cardiovascular reflexes while Jacobsen and Christensen [7] observed that the tachycardia induced by insulin in rabbits was not inhibited by autonomic nervous blockade. How insulin may increase heart rate and contractility is not known but these changes may contribute to the slight hypertensive effect of insulin (see below).

Effects of Changes in Blood Glucose Concentration

A decrease in blood glucose concentration may, in part, be responsible for certain cardiovascular effects observed after administration of insulin. Intravenous injection of insulin (in a dose which did not result in hypoglycaemia) decreased glomerular filtration rate and renal blood flow in diabetic patients [8] but, if the fall in blood glucose was prevented by infusion of glucose, renal blood flow and glomerular filtration rate did not change [8]. Previously, Bröchner-Mortensen showed that intravenous infusion of glucose in normal subjects increased glomerular filtration rate [9], findings which have been confirmed by others [10, 11]. Thus, hyperglycaemia per se is at least partially responsible for the elevated glomerular filtration rate observed in many diabetic patients. Clearly, such hyperfunction is likely to result in structural hypertrophy as observed in the kidneys of diabetic patients and animals. To what extent these early alterations in kidney function may potentiate or cause diabetic glomerulopathy remains a matter for speculation.

Insulin and the Uptake and Release of NA

We and others have observed that intravenous insulin increased plasma NA in subjects with a normal autonomic nervous system [8, 12, 13]. The rise in plasma NA was also observed if blood glucose concentration was kept constant by glucose infusion; plasma adrenaline

Table 1. Acute effects of insulin on cardiovascular function and noradrenaline (excluding effects of hypoglycaemia)

Effects	Mechanisms	Comments
Increase in cardiac contractility and heart rate	Not mediated by changes in blood glucose or catecholamines	Insulin may impair the inotropic action of NA on the heart
Decrease in glomerular filtration rate	Due to the decrease in blood glucose	Opposite changes are seen during hyperglycaemia
Increase in plasma NA	Increase in sympathetic nervous activity	Absent in sympathectomized patients
Arterial hypotension in sympathectomized patients	May be due to attenuated vasoconstrictor activity	Suggests that insulin induces antagonism to the action of NA
Decrease in plasma volume and increase in blood haematocrit	Probably due to the increased release of NA (venoconstriction?)	Absent in sympathectomized patients. More pronounced increments in the haematocrit are observed during hypoglycaemia
Increase in the number of micropinocytotic vesicles in muscle capillary endothelial cells	?	

also did not change [8, 12, 13]. The rise in plasma NA concentration after intravenous administration of insulin is relatively large, nearly as great as the rise in normal subjects during a head-up tilt. Assuming that the rise in plasma NA after insulin reflects an increase in sympathetic nervous activity, one would expect blood pressure to rise considerably as well. However, in subjects with normal reflexes intravenous insulin injection increased arterial pressure only slightly [8]. Plasma NA may increase without a concomitant rise in arterial pressure if the clearance of NA is reduced by insulin or if noradrenaline is released from the adrenal medulla and not from the sympathetic nerve endings; on the other hand arterial pressure may not rise despite an increase in sympathetic nervous activity if there is insulin-induced antagonism to the action of NA.

Plasma clearance of NA has been reported not to change or to increase after administration of exogenous insulin or increments in endogenous insulin release, respectively [13, 14]. Unfortunately, the calculated clearance values in these studies are based on measurements of steady-state NA concentrations in venous rather than in arterial blood. The absolute clearance values reported in these studies are therefore incorrect [15, 16], but nevertheless they make it unlikely that the rise in plasma NA after insulin is due to a reduction in the plasma

clearance of NA. A relatively large increase in plasma NA without associated haemodynamic changes might occur if NA was released from the adrenal medulla. This is, however, an unlikely explanation of the increase in plasma NA because plasma adrenaline did not increase after insulin administration in these experiments [8, 12]. Furthermore, plasma NA rose even in adrenalectomized patients during insulin-induced hypoglycaemia whereas the adrenaline response was completely abolished [17].

A number of studies suggest that insulin may induce antagonism to the action of NA. Several authors have shown that insulin impairs the inotropic action of NA on the heart [4, 5]. Furthermore, insulin may induce a fall in arterial pressure in sympathectomized patients [18–21]. The latter effect of insulin was observed in diabetic patients at a time when the blood glucose was still above normal [20]. In sympathectomized non-diabetic patients the fall in arterial pressure coincides with the fall in blood glucose while in adrenalectomized patients with an intact sympathetic nervous system pulse pressure and mean arterial blood pressure did not change during hypoglycaemia [22]. Seyer-Hansen [23] studied a non-diabetic patient who developed hypotension during meals (post-prandial hypotension). The patient had pronounced autonomic neuropathy and the blood pressure fell during an oral glucose load. Intravenous injection of insulin also resulted in a decrease in arterial pressure although hypoglycaemia did not develop during the test.

In conclusion, these studies indicate that insulin administration increases the release of NA from sympathetic nerves and that this response is not a counter-regulatory response to a decrease in blood glucose concentration. At the same time insulin results in antagonism to the actions of NA.

Mechanisms by Which Insulin Increases NA Release and Causes Antagonism to the Action of NA

Insulin may increase the release of NA through an action on the central nervous system or on the peripheral axon terminals. Rowe et al. [13] suggested that insulin stimulated the sympathetic nervous system through an action on the central nervous system. This hypothesis does not explain the hypotensive effect of insulin. However, the increased release of NA after insulin and the antagonism to NA induced by insulin may be due to entirely different mechanisms. Liang et al. [24] suggested that insulin has a direct dilator effect on skeletal muscle vessels. They considered the rise in plasma NA after insulin to be due to a direct effect of insulin on the central nervous system, whereas the vasodilator effect of insulin was considered to be responsible for the decrease in arterial pressure in sympathectomized patients. The latter hypothesis is not, however, supported by our results in Type 1 diabetic patients. We observed no vasodilator

Table 2. Changes in plasma volume and hematocrit after insulin administration

Authors	Changes observed	Blood glucose	Comments
Gundersen and Christensen 1977 [25]	Plasma volume decreased	Above normal	No changes observed in sympathectomized subjects
MacKay et al. 1978 [26]	Plasma volume decreased. Haematocrit increased	Above normal	
Parving et al. 1979 [28]	Haematocrit did not change	Above normal	The decrease in plasma volume observed was considered to be apparent and due to venous pooling. No changes observed in sympathectomized subjects. Splenectomized subjects showed a normal response, which was not altered by propranolol administration
Frier et al. 1983 [27]	Haematocrit increased	Hypoglycaemia	
Hilsted et al. 1983 (unpublished)	Plasma volume decreased. Haematocrit increased	Hypoglycaemia	
Galbo et al. 1983 [29]	Haematocrit increased	Hypoglycaemia	

response to insulin in man. Forearm blood flow, which to a large extent reflects muscle blood flow, decreased significantly after intravenous insulin [25]. The mechanism of the decrease in forearm blood flow may be due to the fall in blood glucose after insulin (in the same way as a fall in blood glucose concentration decreases renal blood flow [8]) or to the increased release of NA after insulin. Furthermore, because our results were obtained in patients without autonomic neuropathy we cannot exclude the possibility that insulin has a direct vasodilator effect in sympathectomized patients. However, it is clear that an increase in muscle blood flow cannot be responsible for the increase in plasma NA after insulin.

Insulin may act directly on peripheral nerve terminals. Bhagat et al. [5] noted that insulin induced antagonism to NA by enhancing the ability of the tissues to take-up NA. Such a mechanism might explain the hypotensive effect of insulin in sympathectomized patients because plasma NA does not increase after insulin administration in these patients; this abnormality may result in an attenuated vasoconstrictor activity. Although the basal plasma NA appearance rate is reduced, these patients are also more sensitive to the action of NA, i.e. if the tissue uptake of NA is increased and not compensated for by an increase in NA release arterial pressure may fall.

How insulin increases the release of NA and induces antagonism to its actions have thus not been fully clarified. Probably, insulin increases NA release by an action on the central nervous system. The fall in blood pressure in sympathectomized patients after insulin administration is in part because they are unable to increase plasma NA [8, 21]. However, the basic mechanism by which insulin decreases the arterial pressure in these patients has not been fully elucidated but may involve an increase in the tissue uptake of NA.

Changes in Plasma Volume and Haematocrit

Gundersen and Christensen [8, 25] showed that intravenous injection of insulin decreased plasma volume. Several other authors have observed that insulin may decrease plasma volume and increase haematocrit (Table 2). Insulin does not need to cause hypoglycaemia to cause the increase in haematocrit but the increment is larger if it does. It can be seen from Table 2 that the increase in haematocrit did not occur in sympathectomized patients [26, 27]. This suggests that the fall in plasma volume which may occur after insulin is mediated by catecholamines. Intravenous infusion of catecholamines increases the haematocrit or decreases the plasma volume, respectively, either due to an increase in venous tone and capillary pressure or due to an increase in vascular conductance and blood flow [30]. The increase in haematocrit after insulin administration is, however, unlikely to be explained by an increase in blood flow. Frier et al. [27] observed that beta-adrenoceptor blockade with propranolol did not influence the rise in haematocrit after insulin. During insulin-induced hypoglycaemia plus propranolol, or during infusion of adrenaline plus propranolol, forearm blood flow and calf blood flow do not increase [31, 32, 33]. These results suggest that catecholamines released by insulin cause venous constriction, an increase in venous and capillary pressures and thus a loss of plasma volume. Parving et al. [28] concluded that intravenous insulin induced venous pooling and had no effect on plasma volume, because in their experiments the haematocrit did not increase after insulin. This conclusion is unlikely to be correct because several other groups have observed either an increase in the haematocrit or a decrease in plasma volume after insulin (Table 2) and because venous pooling induced by orthostasis or venous stasis is usually accompanied by increased fluid loss from the capillaries.

Capillary Endothelial Cell Morphology After Insulin

Insulin has an effect on muscle capillary endothelial cell morphology in diabetic rats [34]. Ultrastructurally, the endothelial cells appeared normal in short-term streptozotocin-diabetic rats, with the exception of a re-

duced number of free micropinocytotic vesicles. In a controlled study we showed that the number of vesicles was almost normalized 1 h after intramuscular injection of a single dose of insulin. How insulin increased the number of micropinocytotic vesicles in endothelial cells is not clear but our finding may indicate that insulin is essential for normal function of endothelial cells.

Effects of Glucose Administration on NA Release

The rise in plasma NA after insulin does not depend on reduction of blood glucose concentration [8, 13]. It has also been shown that oral glucose increases plasma NA in normal subjects [35–38]. This rise may be due to the increased endogenous insulin secretion. This is likely to be so since intravenous infusion of insulin, in doses that resulted in high physiological increments in plasma insulin, increased plasma NA [13] but the rise in plasma NA after oral glucose was not present in Type 1 diabetic patients [36]. We observed that an oral glucose load increased plasma NA significantly in seven young normal subjects, while it did not change in six age-matched young uncomplicated Type 1 diabetic patients. Furthermore, heart rate and systolic arterial blood pressure increased slightly but significantly in the normal subjects during the test but these changes were not seen in diabetic subjects. It is tempting to speculate that the absence of any rise in heart rate in diabetic patients during the test was due to the lack of change in sympathetic nervous activity. However, we hesitate to draw this conclusion because neither we [7] nor Zwillich et al. [39] could inhibit the increase in heart rate after insulin and glucose administration by beta-adrenoceptor blockade.

Finally it remains possible that the increase in plasma NA and heart rate in normal subjects after oral glucose administration and the lack of corresponding changes in insulin-dependent diabetic patients are due to mechanisms unrelated to plasma insulin concentrations.

In summary, insulin has acute effects on cardiovascular function and plasma NA concentration which are unrelated to the counter-regulatory response to falling plasma glucose concentration. Insulin increases the release of NA from sympathetic nerves and may also induce antagonism to the action of NA. Intravenous insulin decreases plasma volume and increases haematocrit. These effects of insulin are mediated by an adrenergic mechanism (possibly venous constriction) and are absent in sympathectomized patients.

The increase in plasma NA after insulin administration is important because insulin administration may decrease arterial pressure in sympathectomized patients. Plasma NA does not increase in these patients and this may result in attenuated vasoconstrictor activity. The rise in plasma NA after administration of insulin may be a physiological phenomenon since plasma NA increases in normal subjects after an oral glucose load.

Furthermore, during an oral glucose load Type 1 diabetic patients without complications show abnormalities in the regulation of cardiovascular function and sympathetic nervous activity, which may be related to the absent insulin response in these patients. However it cannot be excluded that the increase in plasma NA in normal subjects after insulin administration and after an oral glucose load are due to different mechanisms.

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