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COMMENTARY

Insulin- and glucagon-like peptide-1-induced changes in heart rate and vagosympathetic activity: why they matter

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Abstract Heart rate (HR) predicts cardiovascular morbidity and mortality in individuals either with or without diabetes. In type 2 diabetic patients, cardiac autonomic neuropathy is a risk marker for cardiac morbidity and mortality. A major pathogenic potential may be attributed to vagal depression and sympathetic predominance. In this issue of *Diabetologia*, Berkelaar et al (DOI: 10.1007/s00125-013-2848-6) examined the effects of euglycaemic, and hyperglycaemic clamp with the addition of glucagon-like-peptide-1 (GLP-1) and arginine, on cardiac vagal control in a large number of healthy subjects. After adjustments for age, BMI and insulin sensitivity, insulin associations with HR remained partially intact while those with vagal control disappeared. This suggested that BMI and insulin sensitivity, but not insulin levels, were the main drivers of cardiac vagal control. GLP-1 infusion during hyperglycaemia increased HR and BP and produced a statistically non-significant decrease in measures of cardiac vagal control compared with values before any manipulation of insulin levels. This commentary summarises how, and to what extent, insulin and GLP-1 affect autonomic nervous system activity, HR and BP. More information is needed on the mechanisms through which acute administration of, and long-term treatment with, GLP-1 may affect haemodynamics and autonomic activity in diabetic and obese patients, since this may influence cardiovascular outcomes.

Keywords Blood pressure · Cardiac autonomic neuropathy · GLP-1 · Heart rate · Insulin · Obesity · Type 2 diabetes

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Abbreviations

CAN	Cardiac autonomic neuropathy
GLP-1	Glucagon-like peptide-1
HR	Heart rate
LF/HF	Ratio of low frequency peak/high frequency peak
MSNA	Muscle sympathetic nerve activity

Introduction

An elevated heart rate (HR) is a predictor of cardiovascular morbidity and mortality in individuals with and without diabetes [1–3]. A high HR may result from several factors, including reduced vagal activity or high sympathetic activity. HR variability as assessed by cardiovascular autonomic reflex tests, which largely reflect cardiac vagal control, is lower in diabetic patients and has been recognised as an early marker of cardiac autonomic neuropathy (CAN). Lower HR variability is often observed in patients with recently diagnosed type 2 diabetes, while sympathetic activity is depressed later and causes postural hypotension that is easy to detect [4]. The role of glycaemic control in CAN is supported by DCCT data showing that, in type 1 diabetes, intensive insulin treatment reduced the incidence of CAN by 53% compared with conventional therapy [5]. Similarly, the Steno 2 study showed that, in type 2 diabetic patients, an intensive multifactorial cardiovascular risk intervention reduced the progression or the development of CAN [6].

Reduced HR variability is common in non-diabetic obese patients [7] and in individuals with impaired glucose tolerance [8]. Overweight is a major determinant of HR variability in the general population [9] and is also a major contributor to CAN in patients with type 2 diabetes [10]. In addition, elevated sympathetic activity and diminished vagal activity have been observed in individuals with the metabolic syndrome [11]. Thus, a vagosympathetic imbalance may occur prior to diabetes

as a result of overweight and insulin resistance. This is strongly supported by the recent demonstration that progression to type 2 diabetes is associated with increased central sympathetic drive, blunted sympathetic responsiveness and altered noradrenaline (norepinephrine) disposition [12]. In addition to obesity and diabetes, several factors associated with these conditions, such as insulin, proinsulin, C-peptide, glucose, leptin, adiponectin and NEFA, have been shown to affect the autonomic nervous system [13, 14].

In the Diabetes Prevention Program, randomisation of individuals considered to be at high risk of developing diabetes (BMI 24 kg/m^2, fasting glucose 5.3–6.9 mmol/l, and 2 h glucose 7.8–11.0 mmol/l) to the lifestyle modification arm, which was aimed at weight reduction and engaging in physical activity, improved indices of autonomic function [15]. In overweight individuals, weight loss improved vagosympathetic balance, especially when restriction of energy intake was combined with exercise [16]. Regarding the influence of sympathetic activity in weight loss in obese individuals, higher resting sympathetic drive (as assessed by muscle sympathetic nerve activity [MSNA]) and sympathetic responsiveness to an oral glucose challenge were reported to predict dietary weight loss [17]. Similarly, among obese subjects who had undergone gastric bypass surgery, the greatest reductions in excess body weight were achieved by those observed to have a preserved capacity to shift their cardiac autonomic balance towards a sympathetic predominance during a euglycaemic–hyperinsulinaemic clamp [18].

Pathogenic potential of a vagosympathetic imbalance

Vagal depression and sympathetic predominance are likely to contribute to insulin resistance and a decline in insulin secretion. Moreover, higher HR predicted incident diabetes in the Diabetes Prevention Program [15]. In overweight patients, glucose oxidation rate is negatively correlated with serum insulin levels only in those with cardiac vagal impairment, suggesting that sympathetic overactivity may produce a more severe insulin resistance [19]. In addition, glucose utilisation is negatively correlated with the low frequency/high frequency (LF/HF) ratio on spectral analysis of HR variability, which means that glucose utilisation is reduced when sympathetic activity is predominant [20].

In type 2 diabetic patients, CAN is a risk marker for all-cause and cardiac mortality [21], stroke, coronary events, silent myocardial ischaemia, left ventricular dysfunction, arrhythmia, and nephropathy progression [4]. Sympathetic predominance may account for these disorders and may be involved in the increased risk of cardiovascular events. Regarding the role of vagosympathetic imbalance in hypertension, some data in rats suggest that high vagal activity may protect against obesity-associated hypertension [22]. Other experimental data indicate a link between arterial stiffness and activation of the autonomic nervous system [23]. Both in patients with type 1 and type 2 diabetes, we reported that the prevalence of hypertension increases with CAN severity, which indicates a defect in vagal activity and a relative sympathetic override in hypertension [24]. In line with this, sympathetic activity is greater and baroreflex sensitivity more severely impaired in individuals with obesity and hypertension than in those with either obesity or hypertension alone [25], and similar findings have been observed for individuals with the metabolic syndrome and hypertension [26].

Effects of insulin on vagosympathetic activity

Insulin and glucagon-like peptide-1 (GLP-1) may affect autonomic nervous system activity, HR and BP, and thus potentially alter cardiovascular outcomes. In the present issue of *Diabetologia* [27], Berkelaar et al examined the effects of high levels of insulin on cardiac vagal control in a large series of healthy volunteers with BMIs ranging from 18 to 36 kg/m^2. They used exogenous insulin infusion (euglycaemic–hyperinsulinaemic clamp) and stimulation of endogenous insulin production by different combinations of bolus injections and continued infusion of glucose and other secretagogues (GLP-1 and arginine) to increase levels of insulin up to a mean maximal level of 4,775 pmol/l. At every time point of the experimental protocol, insulin levels were directly associated with HR and inversely related to indices of vagal control. However, after adjusting for age, BMI and insulin sensitivity, the associations with HR remained partially intact, while those with vagal control disappeared. This suggests that BMI and insulin sensitivity, not insulin level, are the main drivers of cardiac vagal control and vagal changes during acute pharmacologically induced hyperinsulinaemia, which is consistent with the well established defect in vagal tone in overweight individuals summarised above.

During the euglycaemic–hyperinsulinaemic clamp, HR and cardiac vagal activity (root mean square of successive differences in interbeat intervals [rMSSD IBI], HF, and peak-valley respiratory sinus arrhythmia, the latter surprisingly low at baseline) did not change significantly [27]. Previous studies have shown a marked increase, a slight increase or no increase in HR during euglycaemic clamps in healthy individuals [28, 29]. Consistent with previous reports [28, 29], HR elevation resulted from vagal depression, but it was also, and probably mostly, produced by cardiac sympathetic activation. Sympathetic activity has been assessed in previous clamp studies by measurement of a variety of variables. These reported that insulin increased MSNA [28, 30], plasma catecholamines [31, 32], and in some studies [29, 33] the LF/HF ratio, which

indicates relative sympathetic predominance. In fact, insulin seems to produce a regionally non-uniform increase in sympathetic activity. Insulin has been observed to increase lumbar but not renal sympathetic nerve activity in animals [34], and to increase sympathetic activity to muscle but not to skin in humans [35]. The sympatho-excitatory effects of insulin result at least in part from a central neural action and possibly from baroreflex activation secondary to peripheral vasodilation induced by insulin [36]. Moreover, the absence of BP changes during hyperinsulinaemia may result from the opposing pressor (mediated by sympathetic activation) and depressor actions (vasodilation) of insulin in the skeletal vasculature.

During the euglycaemic–hyperinsulinaemic clamp the shift in cardiac autonomic nervous system activity towards sympathetic predominance (estimated by the increase in the LF/HF ratio) has been shown to be lower in obese than in lean individuals [33] and depressed in insulin-resistant patients [37]. It is increased in the offspring of insulin-resistant type 2 diabetic patients and absent in the offspring of insulin-deficient type 2 diabetic probands [38]. This suggests that chronic marked hyperinsulinaemia may prevent further enhancement of cardiac sympathetic tone during an acute rise in insulin. A similar trend towards a limited increase in sympathetic activity in obese and type 2 diabetic patients has been reported during other tests, including deep breathing, exercise and oral glucose challenge [12, 39, 40], suggesting a reduction in sympathetic reserve when sympathetic activity is relatively high at baseline. A blunted sympathetic response may result from impaired insulin transport across the blood–brain barrier, which has been shown in experimentally induced insulin resistance in dogs [41], and from lower cerebrospinal fluid insulin levels, as reported in obese insulin-resistant humans [42]. In line with this, brain insulin resistance coexists with peripheral insulin resistance [43, 44].

Effects of GLP-1 on vagosympathetic activity

GLP-1 may also induce changes in haemodynamic variables and modulate autonomic activity. Using a telemetry system, Griffioen et al [45] showed that in mice both acute and chronic central administration of exendin-4, a long-lasting GLP-1 receptor agonist, increased HR and reduced the HF and LF powers of HR variability. Both excitatory glutamatergic and inhibitory glycinergic neurotransmission to preganglionic parasympathetic neurons was diminished, indicating that GLP-1 receptor stimulation may induce changes in HR and HR variability by inhibiting neurotransmission to cardiac vagal neurons. GLP-1, administered peripherally or centrally, has also been shown to increase sympathetic activity in rats [46].

In a small sample of healthy individuals, GLP-1 infusion produced modest but not statistically significant increases in HR (by an average of 3 bpm) and BP and a statistically significant increase in MSNA [47]. However, there were no major modifications in plasma catecholamines or in cardiovagal or cardiosympathetic activity as assessed by spectral analysis of HR variability. In several trials, GLP-1 analogues have been shown to increase the pulse rate of diabetic and obese patients by around 3 bpm [48, 49], indicating that the HR increase persists with long-term treatment, and have been demonstrated to produce a statistically significant decrease in systolic BP, which seems to occur before weight loss [48, 50]. Berkelaar et al [27] investigated GLP-1 infusion in healthy individuals during hyperglycaemia and reported a significant increase in HR of the same magnitude as the aforementioned trials (3 bpm). There was a slight, statistically non-significant decrease in measures of cardiac vagal control compared with those determined before any manipulation of insulin levels. This does not exclude the possibility that GLP-1-induced vagal depression could have been greater in the absence of prior hyperglycaemia and hyperinsulinaemia. Cardiac sympathetic control was not assessed with the power of the LF band or by measuring catecholamine changes, but the data suggested that sympathetic activity was enhanced since HR and systolic BP increased significantly and the double product of HR by systolic BP, a sympathetic activation index, increased accordingly. The increase in HR may be due to the huge increase in endogeneous insulin levels (50-fold increase from baseline to the end of GLP-1 infusion) and insulin-mediated sympathetic activation, or to a proper sympathoexcitatory effect of GLP-1 or a direct effect on the myocardium, where GLP-1 receptors have been shown to be present [51]. C-peptide may also play a role in the regulation of the autonomic nervous system [52], but it is not known whether the action of GLP-1 could be partly mediated by the increase in C-peptide secretion.

More data are needed on the mechanisms through which GLP-1 may affect HR and BP, acutely or during long-term treatment, and further studies on the effects of GLP-1 on haemodynamics and autonomic activity in diabetic and obese patients are required, since this may influence cardiovascular prognosis.

Insulin and GLP-1 share common effects that can contribute to an increase in HR, including vagal depression, sympathetic activation and, possibly, enhancement of the baroreflex secondary to endothelium-induced vasodilation. Both hormones may potentially affect BP in different ways depending on the presence of hypertension, cardiac autonomic impairment and endothelium function. Furthermore, the autonomic nervous system might also affect the haemodynamic response to GLP-1 through its regulatory effect on insulin secretion.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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