Insulin fails to modulate the cardiac L-Type Ca^{2+} current in Type II diabetes patients – a possible link to cardiac dysfunction in diabetes mellitus

Dear Sir,

We have recently shown that insulin increases the L-type calcium current ($I_{Ca,L}$) in human cardiomyocytes in a dose-dependent and reversible manner. Here we report that insulin fails to modulate $I_{Ca,L}$ in human cardiomyocytes of patients with Type II (non-insulin-dependent) diabetes mellitus. The clinical importance of these data is discussed.

Insulin is a crucial regulator of glucose homeostasis and amino acid uptake and plays an important role in cellular physiology. Alterations in insulin availability or impairments of the insulin signalling cascade have been linked to a number of pathologic processes involving the heart. Essential hypertension, cardiac hypertrophy and cardiomyopathy are frequently found in patients with diabetes. Insulin is also known to exert positive inotropic effects in the mammalian heart and in isolated cardiac muscle preparations.

The L-type calcium current ($I_{Ca,L}$) is essential for electromechanic coupling in the heart and plays an important role in cardiac force generation. The positive inotropic action of catecholamines is for example caused – at least in part – by an increased Ca^{2+} influx throught L-type Ca^{2+} channels. We have previously shown that insulin stimulates $I_{Ca,L}$ in rat ventricular and human atrial cardiomyocytes in a dose-dependant and reversible manner at concentrations of 100 nmol/l, 1 μmol/l and 10 μmol/l. Maximal stimulation of $I_{Ca,L}$ was obtained at 10 μmol/l of insulin.

Furthermore, insulin stimulation leads to an increase in cellular cyclic adenosine-monophosphate (cAMP) content and insulin-induced $I_{Ca,L}$ stimulation can be precluded by tyrosine kinase (IRTK) inhibition [1, 2]. Impaired activity of insulin receptor tyrosine kinase has been shown in a variety of tissues from insulin-resistant subjects. Therefore, we hypothesized that insulin action on $I_{Ca,L}$ is mediated by the insulin receptor (IR) and insulin receptor tyrosine kinase involving the adenylyl cyclase/cAMP/protein kinase A (PKA)-second messenger pathway [2].

Here we studied $I_{Ca,L}$ in single human cardiac myocytes from patients with the established diagnosis of Type II diabetes ($n = 7.02$) and patients without diabetes ($n = 14$). The two groups were not significantly different in age, (patients without diabetes vs patients with Type II diabetes (mean ± SD): 65 ± 10 vs 70 ± 7 years). The mean body mass index of patients with Type II diabetes, however, was significantly higher (25.9 ± 2.8 vs 34.6 ± 5.4 kg/m^2, $p = 0.001$). We used the whole cell configuration of the patch-clamp technique to investigate the stimulation of $I_{Ca,L}$ by insulin (10 μmol/l) at room temperature. Right atrial tissue specimens were obtained during cardiovascular surgery and single cardiac myocytes were isolated by enzymatic digestion using collagenase and protease. Cells were voltage-clamped at a holding potential of –50 mV and depolarising pulses to + 10 mV were applied every 10 s to elicit $I_{Ca,L}$. The cell capacity in both groups was not significantly different, 96.2 ± 12.8 pF in D2 and 93.5 ± 13.9 pF in patients without diabetes (n. s.), indicating similar cell size. In addition, there was also no significant difference in the density of $I_{Ca,L}$: 1.5 ± 0.4 pA/pF in D2 vs 1.4 ± 0.2 pA/pF in patients without diabetes.

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In 71 % of the cardiomyocytes from patients without diabetes (10/14) $I_{Ca,L}$ increased following insulin administration (10 μmol/l), whereas only 29 % of the cells isolated from D2 patients (2/7) responded. The average increase of $I_{Ca,L}$ in cells from patients without diabetes was 128.7 ± 62.1 % (range 10.7–211.1 %) and 65.0 % and 146.3 % in the two responsive patients with Type II diabetes. All cells, from both patients with Type II diabetes and patients without diabetes, responded to the administration of isoprenaline (ISO, l0 nmol/l) thereby showing evidence of an intact β-adrenergic pathway.

The increase of $I_{Ca,L}$ following exposure to insulin in cardiomyocyte of patients without diabetes is in accordance with the known positive inotropic effect of insulin. In the majority of patients with Type II diabetes insulin treatment, however, did not induce an increase in $I_{Ca,L}$. The fact that not all cells from patients with Type II diabetes or patients without diabetes responded in the same way, could be due to heterogeneity in the patient population though the group of patients with Type II diabetes is too small for cofactor analysis.

For assessing the clinical relevance of our data and the contribution they make to the understanding of insulin resistance the following findings should be taken into account. Recently it has been shown that plasma cell membrane glycoprotein-1 (PC-1) inhibits IR-tyrosine kinase activity and subsequent cellular signalling. Furthermore, PC-1 content increases in tissue from insulin-resistant subjects and its amount correlates well with the degree of in vivo insulin resistance [3, 4]. Thus, taken together with our previous finding that the insulin effect on $I_{Ca,L}$ is mediated by the IR [2], an increase in PC-1 in our patients with Type II diabetes might be responsible for the impaired response of $I_{Ca,L}$ to insulin. Another important finding giving evidence for a connection between insulin signalling, $I_{Ca,L}$ and cardiac contractility is a series of documented clinical courses of patients with hypodynamic circulatory shock due to severe calcium channel antagonist poisoning. In these reported cases the cardiac shock was not adequately responsive to conventional treatment but after initiation of high-dose insulin-dextrose infusion, the haemodynamic status was stabilized [5].

These known features of insulin action show the clinical relevance of our data and support the view that the proteins involved in IR signal transduction play an important part in the pathophysiology of diabetic cardiomyopathy. Elucidating the mechanisms underlying the Insulin stimulation of $I_{Ca,L}$ will be a highly useful tool in understanding changes in cardiac function in response to metabolic status as well as in studying cardiac pathophysiology of the metabolic syndrome.

Yours sincerely,

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References

1. Aulbach F, Simm A, Maier S et al. (1999) Insulin stimulates the L-type Ca^{2+} current in rat cardiac myocytes. Cardiovasc Res 42: 113–120
2. Maier S, Aulbach F, Simm A et al. (1999) Stimulation of L-type Ca^{2+} current in human atrial myocytes by insulin. Cardiovasc Res 44: 390–397
3. Goldfine ID, Maddux BA, Youngren JF, Frittitta L, Trischitta V, Dohm GL (1998) Membrane glycoprotein PC-1 and insulin resistance. Mol Cell Biochem 182: 177–184
4. Maddux BA, Goldfine ID (2000) Membrane glycoprotein PC-I inhibition of insulin receptor function occurs via direct interaction with the receptor alpha-subunit. Diabetes 49: 13–19
5. Yuan TH, Kerns WP II, Tomaszewski CA, Ford MD, Kline JA (1999) Insulin-glucose as adjunctive Therapy for severe calcium channel antagonist poisoning. Clinisal Toxicology 37: 463–474