Comment on: Krabbe KS, Nielsen AR, Krogh-Madsen R et al (2007) Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 50:431–438

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Received: 13 February 2007 / Accepted: 10 April 2007 / Published online: 2 June 2007
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To the Editor:

Some men see things as they are and say: ‘Why?’
I dream things that never were and say: ‘Why not!’

J. F. Kennedy

In a recent issue of *Diabetologia* Karen Krabbe et al. [1] reported that low plasma levels of brain-derived neurotrophic factor (BDNF) are associated with impaired glucose metabolism in type 2 diabetes, providing a set of supporting data [1], including one of our papers demonstrating reduced plasma levels of both nerve growth factor (NGF) and BDNF in patients with acute coronary syndromes [2]. Thus, Krabbe et al. concluded that decreased BDNF levels (both circulating and those released from brain) may be involved not only in the pathogenesis of dementia and depression [1], but also in diabetes.

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Today, the ‘classical’ neurotrophins NGF and BDNF are increasingly considered not only neurotrophic factors, but also immunotrophins, epitheliotrophins [3] and metabotrophins (metabotropic factors) [4, 5]. Indeed, NGF and BDNF are found in reduced systemic and/or local levels in cardiometabolic diseases such as coronary atherosclerosis, metabolic syndrome and type 2 diabetes [3–5], including various diabetes-associated disorders, such as skin ulcers [3] and erectile dysfunction [6]. Altogether, these data were conceptualised as a metabotrophin-deficit hypothesis of cardiometabolic disease, suggesting novel roles for NGF and BDNF in metabolic and vascular health and disease, that is, their metabotropic potentials, including the improvement of glucose, lipid and antioxidant metabolism [3, 4]. Accordingly, increased BDNF circulating levels documented in cardiometabolic disease [7–9] might be considered a protective phenomenon. Of note: (1) wounded diabetic skin reveals increased levels of NGF, whereas a local treatment with NGF benefits the healing process; and (2) experimentally induced cardiac ischaemia upregulates local NGF levels, whereas exogenously administered NGF improves the cardiac function [3].

Conceptually, both NGF and BDNF are, in analogy to Rita Levi-Montalcini’s semantics of neurotrophic factors, designated metabotropic factors (see text box), a group that also includes adiponectin, interleukin 10, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor and leukaemia inhibitory factor [4]. We hypothesised that stimulation of secretory and/or signalling pathways of metabotropic factors may provide a novel class of drugs in cardiometabolic disease [2–4]. Likewise, one may suggest that sibutramine (a popular anti-obesity drug of the group of serotonin and noradrenaline [norepinephrine] reuptake inhibitors, originally developed as an antidepressant) may,

Metabotropic potential of NGF and BDNF

NGF and BDNF are synthesised and released from pancreatic beta cells
 NGF and BDNF exert insulintropic effect
 NGF and BDNF are protective for the islets of Langerhans
 BDNF improves glucose and lipid profile in experimental diabetes
 NGF upregulates expression of LDL receptor-related protein
 NGF upregulates expression of PPAR- γ
 NGF exerts antioxidant effect
 NGF and BDNF suppress food intake
 NGF improves experimentally induced cardiac ischaemia
 BDNF-deficient mice develop metabolic abnormalities similar to the metabolic syndrome
 An atherogenic diet decreases brain BDNF levels
 Energy restriction increases brain BDNF levels and improves the metabolic profile in experimental metabolic syndrome

Diseases

Reduced NGF and/or BDNF levels*

Coronary atherosclerosis
 Heart failure*
 Acute coronary syndromes*
 Type 2 diabetes*
 Diabetic neuropathy
 Diabetic erectile dysfunction
 Metabolic syndrome
 Obesity
 Bulimia nervosa
 Anorexia nervosa

* There are, however, reports showing elevated circulating levels of BDNF [7–9]

via an increased BDNF brain level [4], mediate its anti-obesity effect. Consistent with this hypothesis are results showing that mutations affecting *Bdnf* (the gene encoding

BDNF) in mice or *NTRK2* (the gene encoding the high-affinity BDNF receptor TrkB) in an 8-year-old boy are associated with hyperphagia and severe obesity [4].

Further studies in the adipobiology and adipopharmacology of metabotropic factors [4] and the role of platelets in the regulation of circulating BDNF levels [10] might support today's promising situation of potential roles of NGF and BDNF in cardiometabolic biology and pharmacology. *Why not?*

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