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Bonding With β-Cells—A Role for Oxytocin in Glucose Handling

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COMMENTARY

The neuropeptide oxytocin is probably best known for its role in social behavior including maternal bonding. It is produced by hypothalamic neurons and plays numerous roles in the central nervous system (CNS) ranging from the establishment of the complex social behaviors over the modulation of neuroendocrine reflexes to the regulation of learning and memory. Over the past decade, oxytocin has also been shown to affect metabolic processes such as food intake and energy homeostasis in animal models (1). More recently, the metabolic effects of oxytocin have been studied in human subjects. Intranasal administration of oxytocin reduces food intake, an effect that seems more pronounced in obese than normal-weight individuals (2,3). Treatment with oxytocin can lead to weight loss and the reversal of weight-related symptoms in obese patients (4). In this issue of *Diabetes*, Klement et al. (5) present evidence that intranasal oxytocin administration modulates insulin/C-peptide secretion and glucose homeostasis in lean, young adults.

Glucose tolerance was tested in 29 healthy, adult men using a double-blind, randomized, and within-subject comparison experimental setup. Subjects consumed the glucose bolus 60 min after intranasal administration of oxytocin or placebo (Fig. 1). Peak blood glucose levels were reduced under oxytocin-stimulated conditions. Under the same conditions, serum insulin and C-peptide concentrations were significantly enhanced 10 min after the glucose bolus. Calculations using the oral minimal model suggest that both the disposition index (the ability of β-cells to secrete insulin when stimulated with glucose) as well as β-cell responsivity (C-peptide levels in correlation to blood glucose levels) are improved when oxytocin is administered. Oxytocin is produced in the hypothalamus and has numerous functions in the CNS. Interestingly, adrenocorticotropic hormone and cortisol levels are not affected under these conditions, suggesting that the observed effects are likely not caused by signaling events along the hypothalamic-pituitary-adrenal axis. Throughout the test, serum oxytocin levels were significantly elevated compared with the placebo regimen. In mice, oxytocin seems to protect β-cells from stress-induced cell death, although oxytocin receptor knockout mice manifest no metabolic anomalies unless challenged with a high-fat diet (6). In this context, it is important to keep in mind that islet architecture and composition is different between humans and mice (7). Importantly, parasympathetic innervation is much more abundant in murine compared with human pancreatic islets (8), making it difficult to translate any findings in mouse models to the human system. Further studies will have to reveal whether oxytocin acts on β-cells directly or indirectly via effects on the CNS in humans.

Because this study supports the oxytocin system as a potential therapeutic target for the treatment of type 2 diabetes (T2D), one important facet will have to be addressed in future studies: the sexual dimorphism apparent both in oxytocin action and metabolic disease. Studies that included women as test subjects showed a sexual dimorphism, related to interactions between steroid hormones (including estrogen and testosterone) and the oxytocin system. Differential effects include social interaction and behavior as well as effects on metabolism and glucose homeostasis. It has been demonstrated that intranasal oxytocin application in women differentially activates brain networks involved in social cognition (9), and estradiol increases plasma oxytocin levels in women (10). In addition, sexual dimorphisms have also long been observed in metabolic disease such as T2D: while T2D incidence is lower in women than in men, hormonal changes during menopause lead to increased disease incidence in postmenopausal women (11). In light of these important differences between men and women, further studies are urgently needed.

In healthy, lean, young men peak levels of blood glucose are attenuated with oxytocin, but after 90 min, there is no discernible difference between oxytocin and placebo treatment. This is probably linked to an enhanced

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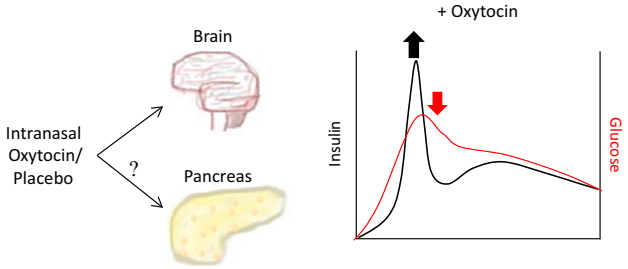

Figure 1—Oxytocin enhances first-phase insulin secretion in healthy young men. Intranasal administration of oxytocin acts either directly or indirectly on pancreatic insulin secretion, leading to enhanced serum insulin and reduced expenditure of blood glucose levels during the first minutes of a glucose challenge.

acute phase of insulin secretion that helps to mobilize glucose across cell membranes and thus lowers circulating blood glucose levels. In this context, it will be important to show that oxytocin can enhance (first-phase) insulin secretion in a (pre)diabetic setting to prove its value as a therapeutic target.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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