

Editorial: The Transformative Age of Leptin in Diabetes Treatment

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Type I diabetes is characterized by the gradual loss of β cells in the pancreas leading to insulin deficiency, hyperglycemia, and if left untreated, death. Since the 1920's Type I diabetes has been treated with multiple daily injections of insulin in an attempt to restore glucose metabolism and stave off ketoacidosis - the life-threatening consequence of chronic hyperglycemia. While insulin injections have allowed millions of people to successfully live with Type I diabetes, it is by no means a perfect treatment. Multiple daily injections and the short half-life of insulin combine to cause daily bouts of hypoglycemia and hyperglycemia, which can cause multiple detrimental sequelae including microvascular damage, nerve damage, fat buildup/obesity, and cardiovascular disease (Smith-Marsh and Zeller 2017). Thus, Type I diabetics have been waiting for a new and better therapy to be developed.

In the 1990s the hormone leptin, a potentially better alternative to insulin, was identified (Zhang et al., 1994). Leptin is released by cells of white adipose tissue and acts on the hypothalamus to regulate glucose metabolism and reduce food intake. Importantly, it is also downstream of insulin. Recent studies show that insulin upregulates levels of leptin (Barr et al., 1997), which then act to negatively regulate insulin, including reducing food intake and β cell insulin production. Together, these two hormones allow for precise regulation of glucose metabolism in healthy adults. Unfortunately, insulinopenia and hyperinsulinemia both result in low levels or activity of leptin leading to inappropriate blood glucose and hyperglycemia (Kalra 2013). Thus, new research into mono treatment with leptin or combined treatment with insulin and leptin is currently underway to provide better options for Type I diabetic patients.

One lab on the forefront of leptin treatment for Type I diabetes is the Shulman lab. Indeed, the

Journal of Postdoctoral Research January 2017 Postdoc of the Month winner, Dr. Rachel Perry, recently published several articles in the Shulman lab regarding the anti-diabetic effect of leptin (Perry et al., 2014; Perry et al., *in press*; Perry et al., 2015). In this month's highlight [article](#), Dr. Perry summarizes her findings on the acute and chronic effects of leptin treatment for restoring euglycemia. In her publication in *Nature Medicine* in 2014, for example, Dr. Perry shows that in addition to numerous reports on the chronic effects of leptin treatment, hyperglycemia is acutely reversed within 6 hours of leptin infusion by suppressing hypothalamic-pituitary-adrenal (HPA) axis activity (Perry et al., 2014), a mechanism that can also explain the actions of fibroblast growth factor (FGF)1 and FGF19 to normalize HPA axis activity (Perry et al., 2015). Dr. Perry defends these findings in the face of a recent article showing no effect of HPA axis regulation on leptin's glucose-lowering activities. She convincingly argues that the lower insulin levels and presence of sucrose water masked the activities of leptin on the hypothalamus in the contrasting study (Perry 2017).

The implications of Dr. Perry's studies are profound. Not only would leptin promote short-term effects in reducing hyperglycemia, thus rescuing those suffering from acute ketoacidosis (Perry et al., *in press*), but it would also provide long-term protection from Type I diabetes and allow precise and effective regulation of blood glucose levels (Wang et al., 2010). Moreover, despite recent doubts on the short-term activities of leptin, the overwhelming majority of studies have indicated a positive effect of leptin treatment on the regulation of hyperglycemia (Perry et al., 2016). The benefits of leptin over insulin are numerous: 1) it has a longer half-life and would only need to be injected 1-2 times a day rather than 3-4 times for insulin, 2) it is downstream of

insulin and therefore allows for tighter regulation of glucose metabolism, 3) precise regulation of glucose metabolism results in fewer troughs and peaks of blood glucose and reduces the harmful side effects of insulin including vascular damage and obesity, and 4) it is anorexigenic, i.e., reduces appetite, and could also be a valuable treatment for Type II diabetes – although there are still potential concerns about leptin resistance in Type II diabetics. There are still potential limitations in leptin therapy including the risk of increased blood pressure, accelerated autoimmune disease, heightened risk of cancer and formation of leptin resistance (Coppari and Bjorbaek 2012). Nonetheless, these risks may be mitigated through additional medications and appear to have a lower incidence rate than the negative side effects of fast-acting insulin.

Even though the majority of clinical trials for leptin therapy are still focused on leptin in dyslipidemia, either in lipodystrophy syndrome or non-diabetic obesity (clinicaltrials.gov), support for leptin treatment in the diabetic community is growing (Nature Medicine 2010) and with more convincing mechanistic studies from Dr. Perry and colleagues, the next decade of Type I and Type II diabetic therapies are sure to be transformative and exciting.

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