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Commentary

Protein-Rich or Amino-Acid Only Diets Entrain the Liver Clock: Time to Scrap Insulin?

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Daily rotation of the Earth on its axis and yearly revolution around the Sun impose periodicity on most organisms. Molecular circadian clocks might have evolved to synchronize internal metabolic rhythms to predictable environmental cycles, in order to most advantageously time functions such as feeding, mating, and general patterns of activity (Tevy et al., 2013). Moreover, a growing body of evidence suggests reciprocal links between nutrient sensing pathway and circadian clocks (Tevy et al., 2013). In mammals, a process integrated by the circadian clock network in mammals is glucose homeostasis (Tevy et al., 2013; Mazzoccoli et al., 2012). The hormones cortisol and melatonin convey the rhythmic output of the suprachiasmatic nucleus (SCN) to peripheral oscillators and modulate glucose homeostasis (Tevy et al., 2013; Mazzoccoli et al., 2012). Circadian rhythmicity of cortisol secretion is implicated in nycthemeral changes of insulin sensitivity (Tevy et al., 2013; Mazzoccoli et al., 2012). Melatonin modulates glucose-stimulated insulin secretion (Tevy et al., 2013; Mazzoccoli et al., 2012). Additionally, peripheral clocks, such as the liver clock, are directly entrained by food and other stimuli, independently of the SCN (Wehrens et al., 2017). Pancreatic insulin production is clearly required in this process. In type 2 diabetes, hitting adults, the body stops responding properly to its own insulin. Type 1 diabetes, characterized by pancreatic islet damage, usually appears earlier, with the dramatic effect of nearly vanished insulin production. Administration of insulin to streptozotocin (STZ)-treated rodents - lacking insulin, a classical animal model of type 1 diabetes - has been shown to restore oscillation of circadian clock genes in rats (Hofmann et al., 2013). Moreover, the liver clock of STZ-treated mice can also be entrained by scheduled feeding (Oishi et al., 2004). Then, how the hepatic peripheral clock of type I diabetic patients can be entrained by food ingestion, in absence of insulin production? A new study by Ikeda et al., published on *EBioMedicine* (Ikeda et al., 2018), attempts to answer to this important medical question. The authors demonstrate, with the help of PER2::LUC bioluminescence, that a protein-only diet and/or cysteine – only among the 20 amino acids - administration, which does not increase insulin levels, elicits entrainment of the liver clock *via* glucagon secretion and/or insulin-like growth factors (IGF-1) production (Ikeda et al., 2018). Moreover, the liver circadian rhythm in STZ-treated mice was altered in response to the intake of a protein-only diet: the latter regimen caused a significant phase advance of the clock genes *Per1*, *Per2*, *Rev-Erbα*, *Bmal1*, and *Dbp*, independently of insulin secretion (Ikeda et al., 2018). Although significant rhythmicity was not reported, circadian clock genes control serum glucagon and IGF-1 levels, as well as hepatic IGF-1 production (Ikeda et al., 2018). These findings suggest for the first time that glucagon and/or IGF-1 production are additional insulin-independent key factors in food-induced entrainment.

Altogether, the data of Ikeda et al. indicate an additional hepatic entrainment that can be applied to chronotherapy by controlling protein-only diet in peoples with diabetes and/or circadian rhythm disorders. Therefore, in some clinical setting, the augmentation of IGF-1, but not insulin, by a protein-rich diet might mediate a beneficial effect on entrainment of liver circadian rhythm. However, strong epidemiological evidence indicate that, independently of age, high protein intake was associated with higher IGF-1 levels and a 5-fold increase in diabetes mortality (Levine et al., 2014). These association studies do not shed light on the long-term mechanistic effects of protein-rich and/or low-carbohydrate diets on diabetes. In this respect, Ikeda et al. propose that the consumption of high-protein food limited to breakfast might entrain peripheral circadian rhythm and prevents obesity (Ikeda et al., 2018). This is consistent with clinical studies showing that in type 2 diabetic individuals, compared with a high-carbohydrate breakfast, the consumption of a high-protein breakfast meal attenuates the postprandial glucose response (Rabinovitz et al., 2014; Park et al., 2015). To our knowledge, no consensus exists about dietary recommendations for diabetic patients, and a wide debate about the nutrient composition in a balanced and healthy diet is still underway in the scientific community. American Diabetes Association (ADA) and National Health Service UK (NHS UK) currently recommend consumption of 50–55 g of proteins per day for all individuals – healthy or diabetics - that accounts for 15–20% of average energy intake from proteins. In agreement with Ikeda et al., both *in vivo* and epidemiological findings suggest the potential role of cysteine supplementation as a low-cost adjuvant therapy in the management of diabetic patients, by controlling glycemic level, lipid profile and oxidative stress (Prasenjit Manna, 2013). Further, pilot randomized controlled clinical trials testing protein- or cysteine-rich diets, and different meal timing/frequency, in individuals affected by type 1 or 2 diabetes are warranted.

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Disclosure of Interest

The author declares no conflict of interest.

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