

Abstract

Obesity and successive comorbidities are estimated to kill over 4 million people per year. Despite considerable advancement in treatment methods, the prevalence of overweight and obesity continues to rise, affecting especially more developed, urban areas. This occurs due to an emergence of the obesogenic environment, composed of highly processed, calorie-dense food and reduced physical activity. In view of this, diet-induced obesity (DIO) has become the most commonly used rodent obesity model, not only to study its consequences, but also the mechanisms underlying various aspects of the disease. Using DIO mice and rats, obesity has been shown to bidirectionally interact with circadian rhythms, on both behavioural and molecular levels, via disrupted feeding and locomotor activity rhythm, as well as misaligned light- and food-entrained oscillators.

Amongst the feeding-responsive central circadian clocks, the Dorsomedial Hypothalamus (DMH) appears the most affected by DIO. The DMH is sensitive to both hunger and satiety signalling molecules, in turn regulating food intake. It is also extremely susceptible to feeding restriction, which potently enhances its oscillatory properties and adjusts the phase of the oscillation so as to enable meal anticipation.

The results of my work confirm a hypothesis, that the DMH is affected by high-fat diet (HFD) even before obesity onset, suggesting that this disruption might partake in the development of the disease. Using electrophysiology and immunohistochemistry I observed the existence of the day/night rhythms in the neuronal activity of the structure, as well as their endogenous (independent of the external cues) nature. HFD-feeding disrupted the rhythmicity of the DMH cells, however this effect was successfully prevented by restricted nighttime feeding, highlighting that this alteration is evoked by the irregular feeding pattern. In view of this, I studied DMH sensitivity to different metabolic states (fasted/fed) with and without regularly scheduled mealtimes. Distinct DMH subdivisions were activated by satiety, depending on whether or not it had been anticipated, which together with an observation of multiple electrophysiological differences between distinct DMH subdivisions, underlines its internal complexity.

In the pharmacological part of the thesis, I studied satiety signalling via the family of the proglucagon-derived peptides (PGDP), since despite the appreciation of the therapeutic potential of the glucagon-like peptide 1 receptor (GLP1R) agonists, not much is known about their mechanism of action upon the hypothalamus. The responsiveness to the PGDP was shown to depend on the level of the spontaneous neuronal activity, but this correlation was abolished

by HFD. Moreover, HFD increased the fraction of cells stimulated by the GLP1R agonist exendin-4 (Exn4), by enhancing the Exn4-evoked level of synaptic activity in the structure. Not only neuronal sensitivity, but also the amount of the PGDP in the structure was affected, with HFD attenuating the metabolic state-dependent changes in the GLP1 immunoreactivity. Differences were not observed when animals had been fed in a restricted manner.

Presented data confirm the presence of a strong connection between obesity and circadian clock disruption, with a desynchronisation of the neuronal oscillatory function occurring even after a short period of HFD-feeding. One of the main reasons for this pathology is an irregular pattern of food intake, which is an important circadian clock synchroniser. The chronobiological aspect of obesity treatment, especially chrononutrition, needs to be given more future consideration, because only a well synchronised circadian timing system, as one of the crucial parts of metabolic health, can slow down the pandemic of overweight and obesity, and their detrimental comorbidities.