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SEROTONIN, A POSSIBLE INTERMEDIATE BETWEEN DISTURBED CIRCADIAN RHYTHMS AND METABOLIC DISEASE

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Abstract—It is evident that eating in misalignment with the biological clock (such as in shift work, eating late at night and skipping breakfast) is associated with increased risk for obesity and diabetes. The biological clock located in the suprachiasmatic nucleus dictates energy balance including feeding behavior and glucose metabolism. Besides eating and sleeping patterns, glucose metabolism also exhibits clear diurnal variations with higher blood glucose concentrations, glucose tolerance and insulin sensitivity prior to waking up. The daily variation in plasma glucose concentrations in rats, is independent of the rhythm in feeding behavior. On the other hand, feeding itself has profound effects on glucose metabolism, but differential effects occur depending on the time of the day. We here review data showing that a disturbed diurnal eating pattern results in alterations in glucose metabolism induced by a disrupted circadian clock. We first describe the role of central serotonin on feeding behavior and glucose metabolism and subsequently describe the effects of central serotonin on the circadian system. We next explore the interaction between the serotonergic system and the circadian clock in conditions of disrupted diurnal rhythms in feeding and how this might be involved in the metabolic dysregulation that occurs with chronodisruption.

Key words: feeding behavior, chronodisruption, serotonin, glucose metabolism, suprachiasmatic nucleus.

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Abbreviations: 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindoleacetic acid; AgRP, Agouti-related protein; ARC, arcuate nucleus; BMI, body mass index; DRN, dorsal raphe nucleus; GABA, γ-aminobutyric acid; IGL, intergeniculate leaflet; L/D, light/dark; MRN, medial raphe nucleus; mRNA, messenger ribonucleic acid; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; SERT, serotonin transporters; SSRI, serotonin reuptake inhibitors; T2DM, type 2 Diabetes Mellitus; TPH, tryptophan hydroxylase.

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INTRODUCTION

The prevalence of obesity has increased progressively over the past decades and this has been linked to several serious medical conditions including Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (Schmidt et al., 2013). In essence obesity is caused by a mismatch between energy intake and expenditure. The brain, especially the hypothalamus, plays a central role in the homeostatic control of energy balance. The hypothalamus not only integrates peripheral signals on energy status, but also orchestrates feeding and autonomic responses to maintain body weight and blood glucose at appropriate levels. To do so different hypothalamic nuclei integrate information from nutrients and related hormonal signals via many neuronal pathways using a variety of (peptidergic) neurotransmitters (Schwartz et al., 2000; Korner et al., 2009).

The basal output of the hypothalamus is not constant but shows diurnal variation. The rhythmicity in output is orchestrated by the biological clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus. In this respect, besides eating and sleeping patterns, glucose metabolism also exhibits clear diurnal variations with higher blood glucose concentrations, glucose tolerance and insulin sensitivity prior to waking up (Carroll and Nestel, 1973; Lee et al., 1992; Kalsbeek et al., 2014) and feeding-induced responses in glucose metabolism depending on the time of day (Kalsbeek and Strubbe, 1998). Although feeding behavior has profound effects on glucose metabolism the diurnal variation in blood glucose concentrations in rats, is independent of the rhythm in feeding behavior (la Fleur et al., 1999; la Fleur et al., 2001).

Generated by pacemaker cells, the SCN has an intrinsic rhythm of a little more than 24 h (in rats and humans), which is synchronized to the exact 24-h rhythm of the environment by the effect of light on specialized photosensitive ganglion cells in the retina expressing the photopigment melanopsin. These ganglion cells directly innervate the SCN via the retinohypothalamic tract (RHT) and indirectly via the geniculohypothalamic tract and the intergeniculate leaflet (IGL) (Gooley et al., 2001). In addition to photic input, the SCN also receives non-photic input on arousal or activity state from the serotonergic cells located in the raphe nuclei either via a direct raphe – SCN projection or indirectly via the IGL (Azmitia and Segal, 1978; Moore et al., 1978; van de Kar and Lorens, 1979; Morin and Meyer-Bernstein, 1999). The SCN projects to a wide range of nuclei, mostly within the hypothalamus, which allows for transferring rhythmic signals to both the autonomic nervous system (ANS) and the hormonal output (Fig. 1) (Kalsbeek et al., 2006). In addition to the central clock in the SCN, circadian oscillators are localized in (almost) all cells of the body, including in organs involved in glucose metabolism, such as the liver, adipose tissue, pancreas and skeletal muscle. The peripheral clocks receive synchronizing signals from the central clock in the SCN, but their main synchronizer seems to be the fasting-feeding cycle (Damiola et al., 2000) which is sufficient to drive the circadian expression of these peripheral oscillators (Kornmann et al., 2007). Thus, diurnal regulation of energy balance and metabolism is dictated by a complex of circadian players, including the SCN, peripheral clocks, and rhythms in light exposure and feeding behavior. In this network light influences the SCN to entrain the organism to the environmental light/dark (L/D) cycle, and the SCN in its turn enables the body to anticipate upcoming events such as awakening in the morning. In addition, feeding itself evokes metabolic and endocrine responses that affect central and peripheral circadian clocks that can respond with either phase-delays or phase-advances according to their phase during exposure (Garaulet and Gomez-Abellan, 2014). When feeding is in synchrony with the environmental L/D cycle, the SCN and the peripheral clocks will be aligned and the body's physiology will be able to anticipate and exert its metabolic and hormonal responses appropriately to the time of the day.

In contrast, feeding in misalignment with the biological clock such as feeding in the dark for humans or during light conditions in rodents will result in conflicting signals to the SCN, because the light conditions are in conflict with the metabolic state. In addition to this discrepancy in input between the central and peripheral oscillators, eating at an inappropriate time point of the day can also cause desynchrony at the level of the SCN because besides photic feedback the SCN also receives non-photic feedback, including non-photic neural feedback derived from serotonin producing cells in the raphe nuclei of the midbrain. The raphe nucleus and serotonin levels themselves are sensitive to nutrients, providing information on which macronutrients are consumed at what time of the day. Thus in diurnal species feeding at night will signal daytime in the SCN via the raphe – SCN projections at times that the (L/D) cycle signals darkness via the RHT (Challet et al., 1997; Mendoza et al., 2005; Challet, 2010; Jang et al., 2012).

We here propose that the observed increased risk for metabolic disturbances in subjects consuming food at inappropriate times of the day (from a SCN point of view) is explained by a mismatch in input from the raphe-SCN and RHT-SCN with a major role for serotonin. We will first review the role of serotonin in feeding behavior and glucose metabolism and subsequently describe the effects of serotonin on the circadian system. We next explore the interaction between these two systems in conditions of misalignment such as eating during night time for humans or during daytime for rodents. We further discuss how this might be involved in metabolic dysregulation.

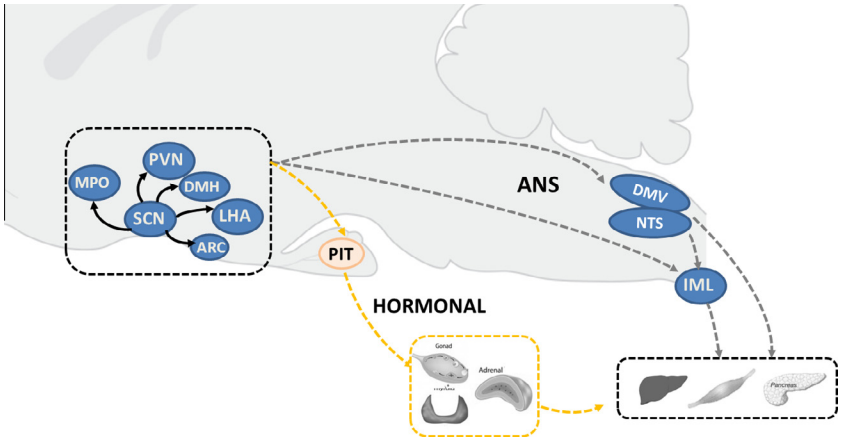

Fig. 1. The SCN projects to a wide range of brain areas to influence both the autonomic nervous system and hormonal output in control of metabolism. SCN = suprachiasmatic nucleus; ARC = arcuate nucleus; MPO = medial preoptic area; PVN = paraventricular nucleus; DMH = dorsomedial hypothalamic nucleus; LHA = lateral hypothalamic area; PIT = pituitary; DMV = dorsomotor nucleus of the vagus; NTS = nucleus tractus solitarius; IML = intermedial lateral column.