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THE HORMONAL CROSSTALKS WITHIN SANTORIO ON HIS WEIGHING CHAIR

Nina MOHORKO
University of Primorska, Science and Research Centre of Koper, Institute for Kinesiology Research, Garibaldijeva 1, 6000 Koper, Slovenia
e-mail: nina.mohorko@zrs.upr.si

ABSTRACT

Santorio Santorio studied metabolism by spending decades seated on a weighing chair, studying the influences of changes in body weight on human health and well-being. Today, metabolism research is oriented toward the hormonal crosstalks which regulate plasma glucose levels, the amount of fat deposits in adipose tissue and feeding. In the search for brain acting metabolism controlling factors, endocrine function has been observed in organs previously not thought of as endocrine organs, such as the stomach and white adipose tissue. The stomach is the main ghrelin secreting organ, while white adipose tissue is the main leptin secreting organ. These two opposing hormones act on the hypothalamus to regulate energy homeostasis – ghrelin in the case of negative energy balance and leptin in the case of the increased amount of fat deposits in adipose tissue. The two hormones display a circadian pattern in their secretion. In fact, the regulation of metabolism is controlled by the circadian clock, but the circadian clock itself is also strongly influenced by food intake.

Keywords: ghrelin, leptin, energy homeostasis, circadian clock

POGOVORI HORMONOV V SANTORIJU NA STOLU-TEHTNICI

IZVLEČEK

Santorio Santorio je preučeval metabolizem tako, da je desetletja preživel na stolu-tehtnici in opazoval vplive sprememb telesne teže na človekovo zdravje in počutje. Danes je raziskovanje metabolizma usmerjeno k navzkrižnim govorom hormonov, ki nadzorujejo nivo glukoze v plazmi, količino maščob v maščevju in prehranjevanje. V iskanju faktorjev, ki nadzorujejo metabolizem in delujejo na možgane, so odkrili endokrino funkcijo v organih, ki jim je prej niso pripisovali, kot sta želodec in belo maščevje. Želodec je glavni organ, ki izloča grelin, belo maščevje pa glavni organ, ki izloča leptin. Ta nasprotujoča si hormona pri nadzoru energijske homeostaze delujeta na hipotalamus – grelin, ko je energijska bilanca negativna, leptin pa, ko se nivo maščobnih odlag v maščevju poveča. Izločanje obeh hormonov ima cirkadiani vzorec. Nasploh je metabolizem nadzorovan s cirkadiano uro, toda tudi sam vnos hranil ima močan vpliv na cirkadiano uro.

Ključne besede: grelin, leptin, energijska homeostaza, cirkadiana ura

INTRODUCTION

”If there daily be an Addition of what is wanting, and a Substraction of what abonds, in due Quantity and Quality, lost Health may be restor’d, and the present preserv’d.” wrote Santorio Santorio about the importance of balance in food consumption in his first aphorism (Santorio, Keill & Quincy, 1720). Santorio spent decades seated on a weighing chair (Figure 1), studying the influence of changes in body weight on human health and well-being. He gathered his observations in his book of aphorisms *De Statica Medicina*, first published in 1614, emphasizing the importance of maintaining a constant weight in the first section of the book. The second edition of *De Statica Medicina* (1615) was reprinted many times (around 40) and was translated into English (1676), Italian (1704), French (1722) and German (1736) (Kuriyama, 2008). Santorio was one of the most important medical doctors in Europe in his time, and was still widely read over a century after his death (Kuriyama, 2008).

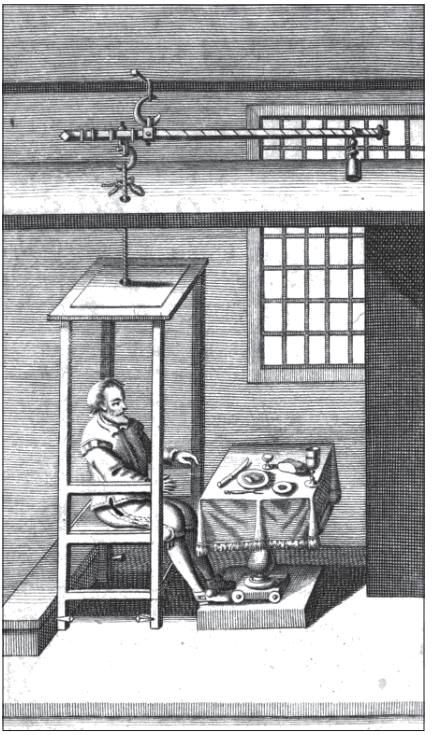

Figure 1: Santorio Santorio on a weighing chair. Frontispiece of De Statica Medicina. From Santorio, S., Keill, J., Quincy, J. (1720). Medicina Statica: being the aphorisms of Sanctorius, translated into English, with large explanations. To which is added Dr. Keil's Medicina Statica Britannica, with comparative remarks and explanations. As also medico-physical essays on [...] by John Quincy. Second edition. London: Printed for W. and J. Newton in Little-Britain, digitized by Google from the library of Oxford University.

Four hundred fifty years after Santorio's birth, the control of body weight is still a subject of scientific research. Scientists have moved away from the use of a weighing chair to measure fluctuations in body weight to research focussed on what happens inside the body: trying to unravel the complicated nature of controlling body weight which has proven to be the sum of multiple metabolic processes, such as whole body energy expenditure, body temperature, locomotor activity, cardio-respiratory parameters and lipogenesis (Gautron & Elmquist, 2011). The metabolic balance is measured in plasma levels of crosstalking hormones and cytokines which are excreted from various tissues and which determine the fate of energy substrates. However, the idea of weighing the food one eats and balancing it with energy consumption has never been so advertised and written about in popular media. An abundance of energy rich food on one side of the scale and a sedentary lifestyle on the other make the import of calories into the daily diet

far higher than the energy expenditure from physical activity. This has led to the obesity epidemic which is of major concern to the World Health Organization since overweight and obesity are the fifth leading risk for death worldwide (WHO, 2011). Furthermore, behavioural sleep deprivation and the disruption of sleep and feeding patterns are found to be alarmingly on the increase within the population, adding to the enhanced life-style-connected all cause morbidity (AlDabal & BaHammam, 2011). This brief paper introduces the complicated network of hormones responsible for the maintenance of body weight. The maintenance of constant of body weight was observed as a characteristic of a healthy person by Santorio Santorio over four centuries ago (Santorio et al., 1720).

Hormonal crosstalk and energy control

The maintenance of a constant body weight is made possible by the regulation of food intake which is a result of a conversation of all the tissues involved in energy metabolism – namely the intestine, pancreas, liver, adipose tissue, muscle and central nervous system through hormonal and neural pathways. While discovering the biochemical fine-tuning of energy homeostasis, endocrine function has been attributed to organs not traditionally thought of as endocrine organs. The interdependence of regulating molecules is especially evident in cases of a disrupted metabolic state, such as in insulin insensitivity and in imbalance in blood glucose levels.

In response to fasting (Asakawa et al., 2001), the stomach secretes a hormone known as ghrelin (Kojima et al., 1999). Ghrelin is a strong appetite inducer (Asakawa et al, 2001; Wren et al., 200l) which promotes increased food intake (Wren et al., 200l). Human plasma ghrelin concentrations fluctuate over the course of the day in relation to food intake (Williams & Cummings, 2005). Ghrelin communicates with the brain through neural afferents from the periphery – the vagus – or by direct action (LeSauter, Hoque, Weintraub, Pfaff & Silver, 2009). Ghrelin receptors (GHS-R) are distributed in the hypothalamus – especially in the arcuate nucleus which also responds to other feeding-control hormones – but also in other brain structures involved in feeding control (Guan et al., 1997). The injection of ghrelin into the fourth ventricle of rats had a hyperphagic effect through brainstem GHS-R, reducing the interval between meals (Faulconbridge, Cummings, Kaplan & Grill, 2003). In the ventral tagmental area, ghrelin has a strong effect on dopaminergic neurons, thus also regulating feeding through the mesolymbic reward system (Abizaid et al., 2006). Outside the nervous system, ghrelin receptor was found in wide range of tissues such as the myocardium, adrenal gland, skeletal muscle, adipose tissue and others (Papotti et al., 2000). Ghrelin administration in humans increased the motility of the proximal gastrointestinal tract (Tack et al., 2006). Recent evidence suggests ghrelin's primary role in energy metabolism during negative energy balance and starvation – being indispensable for blood glucose control during starvation (Briggs & Andews, 2011). Ghrelin potentiates insulin release in the presence of glucose and might function as an anabolic signal molecule during energy depletion (Date et al., 2002). Circulating ghrelin concentration is reduced in dietary induced obesity as are the ghrelin actions which induce increased food intake in the arcuate nucleus of the hypothalamus (Briggs & Andews, 2011). Inactivity

during a five week bed rest experiment caused a drop in plasma ghrelin concentration and an elevation of insulin concentration, independently of energetic balance (Biolo et al, 2008). Apart from the orexigenic properties, the influence on gastric motility and glucose regulation, ghrelin is reported to have antioxidant and anti-inflammatory properties, thus protecting gastric mucosa (Suzuki, Matsuzaki & Hibi, 2011).

In contrast to the orexigenic nature of ghrelin, most food regulating hormones give signals about satiety. White adipose tissue (WAT) is not just an energy repository, but also an active endocrine and secretory organ (Trayhurn & Beattie, 2001). It secrets adipokines, pro-inflammatory cytokines and chemokines such as leptin, adiponectin, resistin, tumor necrosis factor α, interleukin (IL) 1β, IL 6 and others (Federico et al., 2010). The adipokines leptin and adiponectin influence glucose and lipid metabolism and energy homeostasis (Pedrosa et al., 2011) in an opposing manner to ghrelin. Leptin indicates the size of lipid stores in adipose tissue to the hypothalamus (Arch, 2005). Leptin receptors are expressed in many nuclei of the hypothalamus – in the arcuate nucleus, leptin suppresses the neurones with orexigenic activity (Arch, 2005). The concentration of leptin is higher in obese individuals compared to normal weight individuals while the concentration of adiponectin is lower in the obese compared to those of normal weight (Valle, Martos, Gascón, Cañete, Zafra, & Morales, 2005). Plasma leptin level is significantly increased due to inactivity combined with a positive energy balance (Biolo et al., 2008). In obese people, along with elevated plasma leptin concentration, leptin resistance is observed (Arch, 2005). As the latter is also observed in diet induced obesity, leptin might be relatively ineffective in countering hedonistic feeding or might have a plateau above which it is no longer effective (Arch, 2005).

The circadian clock and metabolism

"There are two Kinds of insensible Perspiration, the one is during Sleep, of Humours that are well digested, and after which there is an encrease of Strength: the other is when awake, and arises from indigested Humours, and is weakening more or less, according to the greater or lesser Actions of the Muscles during that Time." explains Santorio (1720) the differences in metabolism between day and night in his Aphorism XX. John Quincy, who translated and commented on Santorio's *De Medicina Statica*, in his explanation to this aphorism states *"... during the relaxed State of the Nerves in sleep, that Secretion which is made in the Brain, and by which they are supply'd with a convenient Juice necessary for their Invigoration [...] Whereas waking, the Vibrations of Pulsations of the Solids, upon which the Motions of the Fluids altogether depend, are more disturb'd and irregular, being subject to Alterations from Abundance of Causes, even from the Thoughts that pass through the Mind; whereby the Juices are more confused, and the Secretions no so perfect [...]"* (Aph. XX, Santorio et al., 1720). Santorio and Quincy observed a difference in metabolism due to changes between day and night. Indeed, changes in the ligh-dark cycle are physiological cues which control food intake, physical activity and the sleep to wakefulness ratio which leads to the evolution of circadian clocks which reflect the 24 hour day in almost all living beings (Gimble, Sutton, Bunnell, Ptitsyn & Floyd, 2011). The circadian clocks try to minimise energy consumption and maximise the chance of survival by an-

ticipating daily-repeating events, and suitably adapt physiology and behaviour to these events. The circadian timing system in the suprachiasmatic nucleus of the hypothalamus is regulated by light and controls the peripheral circadian clocks. Circadian clock-related metabolic regulation in humans is tightly linked to the regulation of sleep (Kovac, Husse & Oster, 2009). Increasing evidence suggests that circadian biology could have a significant effect on the rising incidence of obesity which coincides with the shortened duration of sleep in the general population (Gimble et al., 2011). Both, leptin and ghrelin have diurnal oscillations in their expression. Acute shortage of sleep in healthy subjects resulted in an increased appetite, reduced leptin secretion, increased ghrelin concentration and increased glucose resistance (Spiegel, Tasali, Penev, Van Cauter, 2004). A study on the effect of CLOCK 3111 T/C polymorphism, which governs sleep duration and morningness/eveningness on the ability to lose weight showed that CLOCK 3111 C allele carriers who had a shorter sleep duration and evening preference also had higher ghrelin levels, showed a trend towards overeating and saw reduced weight loss (Garaulet et al., 2011). However, the communication between the circadian clock and metabolism is bidirectional: metabolic processes also give feedback to circadian timing (Kovac et al., 2009). Feeding mice during the day when they normally sleep inversed the phase of their peripheral circadian oscillators (Damiola et al., 2000). The current model of mammalian circadian clocks proposes that they are based on cellular oscillators built from a set of clock genes organised in interlocked transcriptional feedback loops (Kovac et al., 2009). An as yet unidentified endogenous circadian timing system called food-entrainable oscillators (FEOs) functions independently of light to predict the availability of food by activating food-seeking behaviour and enabling the synthesis and secretion of enzymes, necessary for digestion before regularly timed meals (LeSauter et al., 2009). FEOs secrete hormones which are potential regulators of food anticipatory activities and responses that precede food presentation (Silver & Balsam, 2010). Ghrelin expressing oxyntic cells in the stomach express clock genes and are thought to be one of the FEOs (LeSauter et al., 2009).

CONCLUSION

Energy metabolism is regulated by centrally acting hormones excreted from organs which take part in nutrient processing and energy storing. Ghrelin acts in cases of negative energy balance and leptin in cases of an increased amount of fat deposits in adipose tissue. The two hormones display a circadian pattern in their secretion. In fact, the regulation of metabolism is controlled by the circadian clock, but the circadian clock itself is also strongly influenced by food intake – stomach oxyntic cells could be possible food-entrainable oscillators.

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