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A novel neuropeptide Y neuronal pathway linking energy state and reproductive behavior

Yoshikage Muroi *, Toshiaki Ishii

Department of Basic Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido 080-8555, Japan

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ABSTRACT

Animals consume energy for reproduction, as well as survival. Excess or insufficient energy investment into reproduction, respectively, threatens the survival of parents or leads to the failure of reproduction. Management of energy consumption in reproduction is important, not only for the success of the process, but also for the survival of the parents. Reproductive behaviors, such as mating and parental behavior, are indispensable for achieving each event of reproduction including gametogamy, parturition, and lactation. Therefore, reproductive behavior is one of the important factors in managing energy consumption for reproduction. Orexigenic and anorexigenic molecules in the hypothalamus have been implicated in the regulation of reproductive functions. An orexigenic neuropeptide, neuropeptide Y (NPY), has been also implicated in the regulation of both reproduction and energy state of animals. In this review, we will first summarize the neuronal mechanism for regulating reproductive functions by orexigenic and anorexigenic molecules in the hypothalamus. Second, we will focus on the NPY neuronal pathways regulating reproductive behavior in the intra- and extra-hypothalamic brain areas. We will highlight the NPY neuronal pathway from the arcuate nucleus to the dorsal raphe nucleus as a novel extra-hypothalamic pathway for energy state-dependent regulation of reproductive behavior. Finally, we will propose a biological significance of the extra-hypothalamic NPY neuronal pathway, which plays an important role in the associative control of feeding and reproductive behaviors.

Contents

1. Introduction

An appropriate balance between energy intake and its expenditure is essential for the survival of animals. Although, under food-abundant conditions, animals adjust energy intake to meet all of the demands, excess energy intake over its expenditure induces obesity, which increases the risk of various diseases including type 2 diabetes, hypertension, coronary heart disease, cholelithiasis, and sleep-breathing disorders (Kopelman, 2000). On the other hand, under food-scarce conditions, animals need to adjust their energy expenditure to their finite energy intake. Excess energy expenditure decreases body weight and causes malnutrition, leading to starvation in the worst case scenario. Although individual's survival seems to have the paramount priority in animals, animals do not consume their energy only for their own survival, such as thermoregulation, basal metabolism, and maintenance of physical

* Corresponding author.
E-mail address: muroi@obihiro.ac.jp (Y. Muroi).

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activity. Energy investment in reproduction represents energy consumption aimed at non-self. Parents obtain the benefits of transferring their genomic information to the offspring. However, energy investment in reproduction may decrease energy available for the survival of the parents, because all of the reproductive events, including gametogenesis, mating, pregnancy, parturition, and rearing of the young consume parental energy.

The mechanism for energy state-dependent regulation of reproduction has been studied at multiple levels from cells (e.g. gametocytes) to behaviors (e.g., mating behavior and parental care). Lack of balance in energy intake and its expenditure increases the risk of infertility. Excess energy intake over its expenditure causes obesity, increasing the risk of miscarriage and reducing spermatogenesis in humans (Pasquali et al., 2007). Obesity decreases sperm mobility and fertility in male mice (Ghanayem et al., 2010) and pregnancy rates in female mice (Tortoriello et al., 2004). Similarly, negative energy balance also delays the onset of puberty (Kirkwood et al., 1987; Merry and Holehan, 1979) and induces infertility (Evans and Anderson, 2012; Kalra and Kalra, 1996).

Food abundance during the reproductive periods ensures sufficient energy supply to parents, who can partition their energy sufficiently for both their survival and reproduction. In contrast, parents need to restrict the energy partitions of each process, to combine their survival and reproduction under food-scarce conditions. Because animals cannot always obtain abundant food in the wild, they cannot necessarily combine their own survival and reproduction. Under negative energy balance, animals suppress not only their basal activities, but also reproductive activities (Evans and Anderson, 2012; Kalra and Kalra, 1996). These findings suggest that animals regulate reproduction, as well as their basal activities, in an energy state-dependent manner.

Energy partitions are also regulated at multiple levels from cells to behaviors. Regulation of behavior is one of the important mechanisms for managing energy partition, because reproductive behaviors, as well as cellular events such as gametogenesis, are indispensable for achieving each process of reproduction. Reproductive behavior is defined as a series of behaviors aimed at producing or rearing offspring, including search for mate, courtship, mating, childbirth, and rearing of the young. Orexigenic and anorexigenic molecules in the hypothalamus have been implicated as the mediators between energy state and reproductive behavior (Ammar et al., 2000; Bertoldi et al., 2011; Clark, 1995; Inaba et al., 2016; Muroi and Ishii, 2015). Neuropeptide Y (NPY), which is one of the orexigenic molecules released in the hypothalamus in response to negative energy balance (Hahn et al., 1998), has been implicated in the regulation of reproductive behavior under low energy conditions (Inaba et al., 2016; Muroi and Ishii, 2015). Here, we will first review the neuronal mechanism for regulating reproductive functions mediated by a variety of the orexigenic and anorexigenic molecules in the hypothalamus. Secondly, we will focus on the neuronal mechanism for regulating reproductive behavior. We will highlight the NPY neuronal pathways in the intra- and extra-hypothalamic sites. Finally, we will propose a biological significance of the extra-hypothalamic NPY neuronal pathway to control the balance between feeding behavior and reproductive behavior.

2. Orexigenic and anorexigenic molecules in the hypothalamus

The hypothalamus has been studied, as a center for regulating feeding behavior. The orexigenic or anorexigenic neuropeptides have been characterized in the hypothalamus. The arcuate nucleus (Arc) in the hypothalamus, which is located in the proximity of the third ventricle and has less restricted blood-brain barrier (Rodríguez et al., 2010), directly senses the signaling molecules related to the energy status. The Arc contains the neurons co-expressing orexigenic molecules NPY and agouti-related peptide (AgRP) (Hahn et al., 1998), and those co-expressing anorexigenic molecules proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) (Vrang et al., 1999). NPY/AgRP or POMC/CART neurons also release gamma aminobutyric acid (GABA) (Cowley et al., 2001) or both glutamate and GABA (Hentges et al., 2009), as the co-transmitters, respectively. NPY/AgRP neurons innervate POMC/CART neurons to inhibit their activity through GABAergic inputs (Cowley et al., 2001) and NPY inputs via the Y1 receptor (Broberger et al., 1997; Cowley et al., 2001; Fuxe et al., 1997). NPY/AgRP and POMC/CART neurons in the Arc innervate neurons in the hypothalamic nuclei, including the paraventricular nucleus (PVN), ventromedial nuclei of the hypothalamus (VMH), and lateral hypothalamic area (LHA), which also reciprocally project to the Arc (Krashes et al., 2014; Mercer et al., 2011; Sternson et al., 2005). NPY/AgRP and POMC/CART neurons in the Arc also project to the brainstem, including the nucleus of the solitary tract (NTS) and the parabrachial nucleus (PBN) (Jobst et al., 2004). The activities of the NPY/AgRP neurons and POMC/CART neurons are regulated in an energy state-dependent manner. The NPY/AgRP neurons or POMC/CART neurons are activated or inhibited under low energy conditions, respectively (Waterson and Horvath, 2015). Moreover, under low energy conditions, the expression of *NPY* and *AgRP* mRNA (Hahn et al., 1998) or that of *POMC* and *CART* mRNA (Kristensen et al., 1998; Mizuno et al., 1998) also increases or decreases, respectively.

3. The mechanism for detecting energy state by NPY/AgRP neurons and POMC/CART neurons

NPY/AgRP and POMC/CART neurons directly detect nutritional molecules including glucose (Thorens, 2012) and fatty acids (Jo et al., 2009). Glucose-sensing neurons were first identified by Anand et al. (Anand et al., 1964). They were classified into two groups, glucose-excited and glucose–inhibited neurons, which increase and decrease their activities in response to glucose concentration, respectively (Thorens, 2012). Glucose directly inhibits NPY/AgRP neurons (Lee et al., 2005; Parton et al., 2007) and activates POMC/CART neurons (Ibrahim et al., 2003). Glucose also regulates the synthesis of neurotransmitters, such as AgRP (Chalmers et al., 2014). Furthermore, NPY/AgRP and POMC/CART neurons also detect the energy state via hormones released from the peripheral tissues in response to the energy levels (MacDougald et al., 1995; Toshinai et al., 2001). Ghrelin is an orexigenic hormone released from stomach under low energy conditions (Kojima et al., 1999), whereas leptin is an anorexigenic hormone originating from adipose tissue under energy-rich conditions (Zhang et al., 1994). Insulin is also an anorexigenic hormone secreted from beta cells of the pancreas (Lois and Kumar, 2009). The majority of NPY/AgRP and POMC/CART neurons in the Arc express leptin receptor, leptin receptor (LepR) (Baskin et al., 1999; Cheung et al., 1997; Baskin et al., 1999), and ghrelin receptor, growth hormone secretagogue receptor (GHSR) (Baskin et al., 1999; Cheung et al., 1997; Quennell et al., 2009). These neurons also express insulin receptors (Benoit et al., 2002; Könner et al., 2007; Marks et al., 1992). Ghrelin activates NPY/AgRP neurons (Andrews et al., 2008; Cowley et al., 2003), and inhibits POMC neurons (Cowley et al., 2003). Conversely, leptin (van den Top et al., 2004) and insulin (Könner et al., 2007; Qiu et al., 2014) inhibit NPY/AgRP neurons. Although leptin activates POMC/CART neurons (Cowley et al., 2001; Hill et al., 2010; Williams et al., 2010), insulin has been reported to inhibit POMC/CART neurons (Hill et al., 2010; Williams et al., 2010). Because leptin and insulin have anorexigenic effects, their antagonistic effects on POMC/CART neurons have been a long-standing enigma. Qiu et al. (2014) reported that the inhibitory effect of insulin on POMC/CART neurons is due to the zinc contained within the insulin formulation. In fact, they demonstrated that insulin by itself activates POMC/CART neurons.

4. The regulation of gonadotropin-releasing hormone neurons by NPY/AgRP and POMC/CART neurons

The hormonal mechanism, by which NPY/AgRP and POMC/CART neurons detect energy state, has been implicated in the regulation of