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

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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.

**Keywords**

Neuropeptide Y, hypothalamus, dorsal raphe nucleus, reproductive behavior

## 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 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, 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, 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. Qui 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 reproductive functions. NPY/AgRP (Li et al., 1999) and POMC/CART (Leranth et al., 1988) neurons form the synapses with gonadotropin-releasing hormone (GnRH) neurons, and directly regulate the activity of GnRH neurons (Roa and Herbison, 2012). NPY neurons directly innervate GnRH neurons (Li et al., 1999; Roa and Herbison, 2012) to inhibit their activity (Roa and Herbison, 2012). POMC/CART neurons also directly project their axons to GnRH neurons (Backholer et al., 2013; Cravo, et al., 2011; True et al., 2013). Alpha-melanocyte-stimulating hormone (α-MSH), which is one of the proteolytic cleavage products of POMC, activates GnRH neurons via melanocortin receptors type 3 and 4 (Roa and

Herbison, 2012). Although GnRH neurons express no LepR (Cunningham et al., 1999; Quennell et al., 2009), the intraperitoneal injection of leptin increases GnRH secretion in rats (Reynoso et al., 2003). Leptin also increases GnRH-stimulated release of luteinizing hormone (LH) in LbetaT2 gonadotropes (Avelino-Cruz et al., 2009), indicating that NPY/AgRP and POMC/CART neurons mediate leptin-induced GnRH secretion.

In contrast to leptin, ghrelin directly regulates the activity of GnRH neurons via GHSR (Farkas et al., 2013). Ghrelin decreases GnRH secretion (Fernández-Fernández et al., 2005; Lebrethon et al., 2007), followed by the decrease in the release of LH (Fernández-Fernández et al., 2005; Martini et al., 2006) and FSH (Fernández-Fernández et al., 2005; Furuta et al., 2001; Martini et al., 2006). Furthermore, NPY/AgRP and POMC/CART neurons also express GHSR (Kristensen et al., 1998; Willesen et al., 1999). Thus, ghrelin directly and indirectly regulates the activity of GnRH neurons. Moreover, insulin also directly regulates the activity of GnRH neurons. Although GnRH neuron-specific deletion of insulin receptor had no effect on puberty timing and fertility in lean mice (Divall et al., 2010), the deletion improved fertility in mice with diet-induced obesity (DiVall et al., 2015), indicating that insulin receptor signaling in GnRH neurons is involved in the infertility of obese mice.

The suppression of reproductive functions under low energy conditions has been

implicated in the inhibition of gonadal functions. Food restriction inhibits the release of GnRH, followed by the decrease in the levels of LH and FSH (Aloi et al., 1997; Bergendahl et al., 1991; Cameron et al., 1991; Campbell et al., 1977). NPY/AgRP and POMC/CART neurons regulate the activity of GnRH neurons, not only directly, but also indirectly via kisspeptin neurons. The kisspeptin neuronal system has been studied, as the link between energy balance and reproduction (De, Bond, and Smith, 2014; Wahab et al., 2013). Kisspeptin neurons are distributed in the Arc and the anterior periventricular nucleus in rodents (Brailoiu et al., 2005; Shahab et al., 2005; Ramaswamy et al., 2008; Wahab et al., 2011). The kisspeptin receptor (Kiss1r) is expressed in various regions of the central nervous system including the striatum, hippocampus, hypothalamus, and amygdala (Kotani et al., 2001; Shibata et al. 2007), and in the peripheral tissues, including placenta and pancreas (Kotani et al., 2001; Lee et al., 1996; Muir et al., 2001; Ohtaki et al., 2001). GnRH neurons express kisspeptin receptors (Han et al., 2005; Irwig et al., 2004; Smith et al., 2008). Neuronal fibers immunoreactive to kisspeptin appose to the GnRH neuronal cell bodies or fibers (Clarkson and Herbison, 2006; Kinoshita et al., 2005; Smith et al, 2008). Administration of kisspeptin induces the release of GnRH in vivo (Han et al. 2005; Irwig et al., 2004; Messager et al., 2005). Kisspeptin directly activates GnRH neurons (Han et al., 2005; Irwig et al., 2004; Messager et al., 2005; Pielecka-Fortuna et

al., 2008) to induce LH and FSH secretion (Han et al. 2005; Irwig et al., 2004; Messager et al., 2005). Thus, kisspeptin neurons increase the activity of GnRH neurons.

The intracerebroventricular injection of NPY decreases GnRH secretion in vivo (Catzeflis et al., 1993; Kalra, 1993). However, it has not been clarified whether NPY directly regulates kisspeptin neurons (De, Bond, and Smith, 2014). In contrast to NPY, POMC and CART directly regulate kisspeptin neurons. Kisspeptin neurons express melanocortin receptor type 4 (Cravo et al., 2011). Moreover, CART depolarizes kisspeptin neurons in the Arc (True et al., 2013), indicating that POMC/CART neurons activate kisspeptin neurons to increase GnRH neuronal activity. Otherwise, kisspeptin neurons directly mediate the signaling of leptin, insulin, and ghrelin to regulate GnRH neuronal activity. Kisspeptin neurons express lepR (Backholer et al., 2010; Smith et al., 2006), insulin receptor (Qiu et al., 2013), and GHSR (Frazao et al., 2014).

## 5. The regulation of reproductive behavior by NPY/AgRP and POMC/CART neurons

As well as gonadal function (Bronson, 1990), energy state also affects reproductive behavior, including the search for mate, courtship, mating, and rearing of the young. Food restriction delays puberty (Kirkwood et al., 1987; Merry and Holehan,

1979), suppresses sexual behavior in both sexes (Gill and Rissman, 1997; Inaba et al., 2016; Klingerman et al., 2013; Sabau and Ferkin, 2013), inhibits maternal care (Andrews and Rosenblum, 1991; Muroi and Ishii, 2015), and advances the termination of lactation in dams (Eillen 1991). Orexigenic and anorexigenic molecules have also been implicated in the regulation of reproductive behaviors. Subcutaneous or intraventricular treatment with orexigenic molecules suppresses reproductive behavior, while treatment with anorexigenic molecules facilitates reproductive behavior. In rodents, NPY (Ammar et al., 2000; Clark et al., 1985; Inaba et al., 2016) and ghrelin (Bertoldi et al., 2011) inhibit sexual behavior, whereas leptin (Ammar et al., 2000; Wade, et al., 1997) and α-MSH (Thody et al., 1979; Thody et al., 1981) stimulate sexual behavior. Moreover, NPY decreases (Muroi and Ishii, 2015) while leptin increases (French et al., 2009) maternal behavior.

One mechanism for regulating reproductive behavior by orexigenic or anorexigenic molecules may be the regulation of the hypothalamic-pituitary-gonadal (HPG) axis via the regulation of GnRH secretion. This possibility is supported by the finding that gonadoectomy-induced inhibition of reproductive behavior can be recovered using hormonal treatment. Although gonadoectomy disrupts sexual behavior, hormonal treatments can improve it in both sexes of rodents (Cross and Roselli, 1999; Hardy and

DeBold, 1976; Henrik and Gerall, 1976; Hull and Dominguez, 2007; Krey and McGinnis, 1990; McGinnis and Dreifuss, 1989; Muroi et al., 2006). Although the level of testosterone in the serum reaches undetectable value by 24 h after castration (Krey and McGinnis, 1990), male rats can display mounting, intromission, and ejaculation even a few weeks after castration (Davidson, 1966). These findings indicate that gonadal hormones regulate reproductive behavior slowly, possibly via genomic regulation. On the other hand, the treatment with estradiol improves chemoinvestigation and mounting behavior in castrated males within 35 min (Cross and Roselli, 1999). Thus, the gonadal hormones can also rapidly exert their effect on rats, possibly via the membrane receptors (Schwartz et al., 2016). Repeated exposure to pups can induce maternal behavior in virgin females of rats and mice. Hypophysectomy and ovariectomy does not affect maternal behavior in virgin female rats (Rosenblatt, 1967) and mice (Leblond and Nelson, 1937), indicating that gonadal hormones may not be involved in regulating the basal level of maternal responsiveness. However, changes in estrogen (Rosenblatt and Siegel, 1975) and progesterone (Bridges et al., 1978) levels before delivery affect the onset of maternal behavior in rats. The increase in estrogen levels and the steep decrease in progesterone levels toward the end of pregnancy shorten the latency to the onset of maternal behavior in ovariectomized nulliparous rats (Bridges, 1984; Moltz et al., 1970). Implantation of

estradiol into the medial preoptic area, which is indispensable for regulating maternal behavior (Tsuneoka et al., 2013), also facilitates the onset of maternal behavior (Fahrbach and Pfaff, 1986; Numan et al., 1977). Therefore, gonadal hormones may be required for displaying maternal behavior, when dams are exposed to pups for the first time, namely at the first parturition, and they may not be required for the instant regulation of maternal behavior. On the other hand, cats hypophysectomized during the gestational period, showed no maternal care, even though the delivery was normal (Allan and Wiles, 1932). Although orexigenic or anorexigenic molecules may regulate reproductive behavior through the HPG axis, their role may be different for different aspects of reproductive behaviors, the timing of their expression, and the species.

Another mechanism is that orexigenic or anorexigenic molecules directly regulate the neuronal activities involved in the regulation of reproductive behaviors. Direct injection of the agonist or antagonist against the receptors for NPY into the DRN or ghrelin into the laterodorsal tegmental area or the ventral tegmental area affects sexual (Inaba et al., 2016; Prieto-Garcia et al., 2015) or maternal behavior (Muroi and Ishii, 2015). In the next section, we will focus on the NPY neuronal pathway, which directly regulates the neuronal activities involved in the control of reproductive behavior.

## 6. The regulation of reproductive behavior through the extra-hypothalamic NPY neuronal pathway

NPY is expressed in a variety of brain regions (Allen et al., 1983; Chronwall et al., 1985; Danger et al., 1990; de Quidt and Emson, 1986). NPY-positive cell bodies are distributed in the cortex, striatum, amygdala, and hippocampus, whereas the fibers are distributed in the locus coreuleus, periaqueductal gray (PAG), nucleus raphe pallidus, and ventral tegmental area. NPY has been implicated in a variety of physiological functions including anxiety, circadian rhythm, learning, and thermoregulation (Bi et al., 2013; Borbély et al., 2013; Heilig, 2004; Morin, 2012). These multiple functions are mediated via the five types of receptors, which are classified into Y1, 2, 4, 5, or 6 (Michel et al., 1998). All types are coupled with trimetric $G_{i/o}$ protein.

NPY/AgRP neurons in the Arc form the intra-hypothalamic and extra-hypothalamic pathways (Betley et al., 2013; Broberger et al., 1998). Within the hypothalamus, the NPY/AgRP neurons innervate the PVN, LHA, and VMH (Mercer et al., 2011; van Swieten et al., 2014), which are the second order structures involved in feeding behavior. In addition to these orexigenic pathways, another intra-hypothalamic NPY neuronal pathway has been characterized, as the reproductive pathway (Kalra and Kalra, 1996) that regulates the HPG functions as mentioned above (Celik et al., 2015; De

Bond et al., 2014; Nestor et al., 2014; Wahab et al., 2013).

We recently reported that NPY signaling in the dorsal raphe nucleus (DRN) is involved in energy state-dependent regulation of maternal behavior (Muroi and Ishii, 2015) and male sexual behavior in mice (Inaba et al., 2016). The DRN is located in the midbrain and receives innervation from many brain regions, including the medial prefrontal cortex, lateral habenula, and hypothalamus (Soiza-Reilly and Commons, 2011). The DRN contains a large number of serotonergic neurons, which project their axons to various brain regions, including the olfactory bulb, cortex, hippocampus, hypothalamus, and amygdala (Michelsen et al., 2007). The DRN has also been implicated in a variety of physiological functions, including cognition, sleep, circadian rhythms, reward, and pain (Zhao et al., 2015), and pathological functions, including anxiety disorder, depression, and panic disorder (Paul et al., 2014; Paul and Lowry, 2013). Previous studies reported that AgRP-positive neurons project from the Arc into the PAG (Betley et al., 2013; Broberger et al., 1998), which is located in the midbrain dorsolaterally to the DRN. Moreover, the immunohistochemical analysis indicated that AgRP-positive fibers are also distributed in the dorsal part of the DRN (Betley et al., 2013). AgRP neurons in the Arc coexpress NPY (Hahn et al., 1998), and some of the NPY neurons in the Arc project to the DRN (Yoon et al., 2013). NPY-immunopositive neuronal processes are also

distributed in the PAG and the dorsal part of the DRN (Inaba et al., 2016; Muroi and Ishii, 2015; Yoon et al., 2013). We asked whether NPY-positive neuronal processes form synapses in the DRN. A presynaptic marker, synaptophysin, was colocalized with NPY in the dorsal part of the DRN in mice (Inaba et al., 2016; Muroi and Ishii, 2015), indicating that NPY neurons form synapses in the DRN. The *Y1*, *2*, and *5* receptor mRNA are also expressed in the DRN of rats (Durkin et al., 2000; Parker and Herzog, 1999). The Y1 and Y2 receptors regulate neuronal activities in the DRN (Díaz-Cabiale et al., 2011; Durkin et al., 2000). Therefore, we examined whether NPY signaling into the DRN is involved in some physiological functions in an energy state-dependent manner.

First, we examined whether NPY signaling into the DRN is involved in energy state-dependent regulation of maternal behavior in mice (Muroi and ishii, 2015). Food deprivation for 9 h inhibits maternal behavior including nest maintenance, pup retrieval, and crouching behavior in dams. Direct injection of NPY into the DRN inhibited the expression of maternal behavior in free-fed dams, whereas an antagonist to the Y1 receptor, BIBP-3226, recovered maternal behavior in fasted dams. The Y1 receptor was expressed in serotonergic neurons or GABAergic interneurons in the DRN. These results indicate that NPY inhibits neuronal activity via the Y1 receptor, because this receptor has an inhibitory effect on cellular activity (Nakamura et al., 1995; Thorsell, 2010). The

pharmacological treatments to suppress serotonergic neuronal activity or GABAergic signaling, also inhibited maternal behavior in free-fed dams, while the treatments to increase the activity of serotonergic neurons or GABAergic signaling improved maternal behavior in fasted dams (Muroi and Ishii, 2015). These results suggest that NPY signaling in the DRN mediates the suppression of maternal behavior under low energy conditions. These findings may seem contradictory because GABAergic neurons inhibit the activity of serotonergic neurons in the DRN. The temporal pattern and the intensity of serotonergic neuronal activation affect the responses of neurons receiving serotonergic innervation (Gartside et al., 2000; Puig et al., 2005). Because $GABA_B$ receptor-mediated GABAergic signaling can regulate the activity of serotonergic neurons in the DRN in an inhibitory or excitatory manner (Abellán et al., 2000), GABAergic modulation is important for regulating serotonergic neuronal activity. NPY may inhibit serotonergic neuronal activity and reduce GABAergic signaling. This, in turn, would suppress maternal behavior.

Similar results were obtained for male sexual behavior in mice (Inaba et al., 2016). Fasting for 24 h inhibited male sexual behavior including mounting, intromission, and ejaculation. Direct injection of NPY into the DRN inhibited the expression of sexual behavior in free-fed males, whereas BIBP-3226 recovered sexual behavior in fasted males.

Direct injection of (±)-8-hydroxy-2-dipropylaminotetralin, which is a 5-$HT_{1A}$ receptor agonist that inhibits the activity of serotonergic neurons, into the DRN inhibited sexual behavior in fed males, while (+)-DOI hydrochloride, a 5-$HT_{2A/2C}$ receptor agonist that activates serotonergic neurons, recovered sexual behavior in fasted males. These results suggest that NPY signaling in the DRN also mediates the suppression of sexual behavior under low energy conditions.

These findings suggest that NPY signaling into the DRN is involved in energy state-dependent regulation of maternal behavior and male sexual behavior, and that the inhibition of serotonergic neurons by NPY results in the suppression of those behaviors. Serotonin has been implicated in reproductive behavior, including maternal behavior (Alenina et al., 2009; Lerch-Haner et al., 2008; Zhao and Li, 2010) and sexual behavior (Rubio-Casillas et al., 2015; Snoeren et al., 2014; Uphouse, 2014). However, the way, in which serotonergic neurons in the DRN regulate reproductive behavior, is complicated to understand. Serotonergic neurons in the DRN project to a variety of brain regions including the olfactory bulb, cortex, hippocampus, hypothalamus, and amygdala (Michelsen et al., 2007). Serotonin receptors are classified into seven subtypes containing at least thirteen members (Hannon and Hoyer, 2008). Serotonin can increase or decrease the activities of identical neurons via different members of the serotonergic receptor

family (Hori et al., 1996; Huang and Kandel, 2007). At the behavioral level, different serotonin receptors also have a stimulatory or inhibitory effect on the identical parameter of sexual behavior, such as lordosis of female rats (Uphouse, 2014). Moreover, an identical member of the serotonergic receptor family, 5-$HT_{1A}$, regulates different parameters of reproductive behavior, such as copulatory and ejaculatory behaviors in male rats (Snoeren et al., 2014). Thus, different serotonin receptors regulate different parameters of reproductive behavior in a many-to–many relationship. Moreover, histochemical studies demonstrated that different members of the serotonin receptor family overlap in their distribution (Shukla et al., 2014; Wirth et al. 2016). Because each receptor utilizes different signaling pathways (Hannon and Hoyer, 2008), the overlap of the receptor expression also generates the diversity of the signal transduction. For example, 5-$HT_{4B}$ receptor increases or decreases the cellular activity, depending on the activity of protein kinase A (Cai et al., 2002). Thus, the intracellular signaling also increases the diversity of the regulation by the serotonergic signaling. More research is required to clarify how serotonergic neurons in the DRN mediate energy state-dependent regulation of reproductive behavior.

## 7. Conclusion

NPY/AgRP neurons in the Arc innervate the extra-hypothalamic nuclei: the NTS, PBN, and PAG (Broberger et al., 1998). In rats, NPY regulates the cardiovascular functions in the NTS (Díaz-Cabiale et al., 2007; Tai et al., 2007), and mediates anti-nociceptive effect (Wang et al., 2000, 2001) and anxiolytic effect (Kask et al., 1998a, b) in the PAG. It has been unclear whether these pathways are associated with feeding behavior. We propose that the NPY neuronal pathway from the Arc to the DRN regulates reproductive behavior in the association with feeding behavior, as follows: NPY neurons in the Arc are activated under low energy conditions. Some of the NPY neurons transduce their signals into the PVN, VMH, and LHA to stimulate feeding behavior, whereas others transduce their signals into the DRN to inhibit reproductive behavior (Fig. 1). These pathways control the energy partition at the behavioral level, leading to prioritizing of feeding behavior over reproductive behavior, under low energy conditions.

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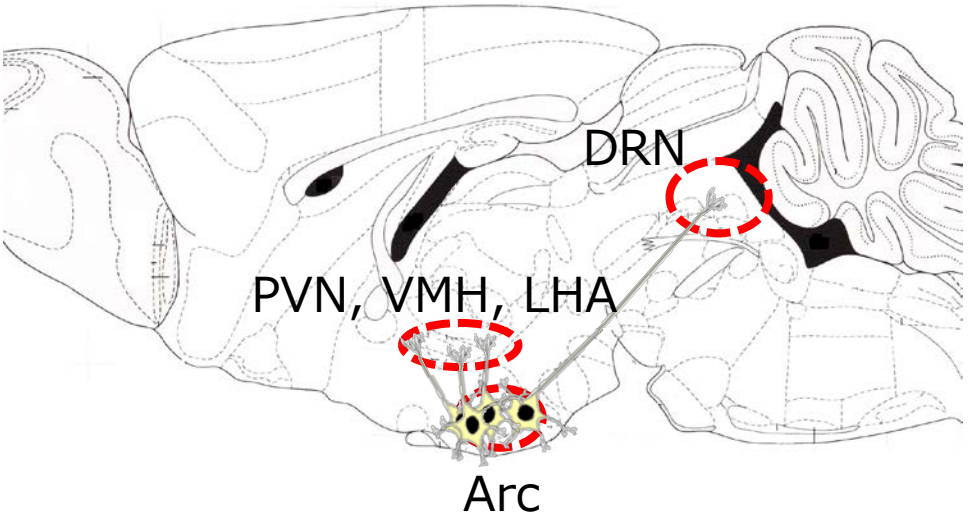
**Figure captions**

A diagram showing the NPY neuronal pathways from the Arc that coordinate feeding and reproductive behaviors. NPY neurons in the Arc are activated under low energy conditions. Some of the NPY neurons transduce their signals into the PVN, VMH, and LHA to stimulate feeding behavior, whereas others transduce their signals into the DRN to inhibit reproductive behavior.

Figure 1




Under low energy conditions

↓

NPY neuronal activity in the Arc ↑

↓ PVN, VMH, LHA → Feeding behavior ↑

↓ DRN → Reproductive behavior ↓