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Energy homeostasis and reproduction require tight coordination, but the mechanisms underlying their interaction are not fully understood. Two sets of hypothalamic neurons, namely pro-opiomelanocortin (POMC) neurons in the arcuate nucleus and steroidogenic factor-1 (SF1) neurons in the ventromedial hypothalamic nucleus, are emerging as critical nodes where metabolic and reproductive signals communicate. This view is supported by recent genetic studies showing that disruption of metabolic signals (e.g., leptin and insulin) or reproductive signals (e.g., estradiol) in these neurons leads to impaired regulation of both energy homeostasis and fertility. In this review, we will examine the potential mechanisms of neuronal communication between POMC, SF1, and gonadotropin-releasing hormone neurons in the regulation of metabolism and reproduction.

Keywords: hypothalamus, energy homeostasis, reproduction

INTRODUCTION

Since animals under metabolic stress must invest their energy in survival rather than reproduction, the reproductive axis has the capacity to respond to changes in caloric status. The hypothalamic signals driving the reproductive axis are suppressed when a mammal is in negative energy balance, whether that state is caused by inadequate food intake, excessive locomotor activity, or heavy thermoregulatory costs. Likewise, the energy demands of maintaining fertility and successful reproduction require increased food consumption and appropriate regulation of energy expenditure. Therefore, hypothalamic control of metabolism must be responsive to the reproductive state of the animal. However, despite the passage of 40 years since the discovery of gonadotropin-releasing hormone (GnRH; Schally et al., 1971), the afferent neuronal groups and pathways through which gonadal steroids and nutrient signals regulate GnRH release remain unresolved.

Much attention has focused on the role of hypothalamic neurons expressing kisspeptin in coordinating GnRH neuronal function and the physiological state of the animal. However, while the central role of kisspeptin in steroid feedback to the hypothalamus is clear, evidence of it conveying metabolic signals to the reproductive axis is equivocal. In addition, data suggest that other hypothalamic neurons also convey gonadal steroid input to GnRH circuitry, either directly or via the kisspeptin network.

Here we will discuss new findings resulting from genetically modifying pro-opiomelanocortin (POMC) and steroidogenic factor-1 (SF1) neurons of the hypothalamus. While primarily understood to function as metabolic regulators, these neurons are emerging as critical nodes of communication that respond to both metabolic and reproductive cues and directly interact with reproductive circuitry. In particular, we will focus on their ability to transmit information gleaned from circulating factors, specifically leptin, insulin, and estradiol (Figure 1).

CANONICAL REPRODUCTIVE CIRCUITS

Hypothalamic GnRH neurons produce the final output of a complex neuronal system regulating fertility. Adult mammals possess a loose field of GnRH neurons stretching from the olfactory bulbs to the medial basal hypothalamus with a highly dense population of GnRH neurons within the preoptic area (POA) and adjacent to the organum vasculosum of the lamina terminalis (OVLT). The axons of GnRH neurons project to the median eminence (ME) where GnRH is secreted in pulses into the pituitary portal bloodstream. GnRH neurons can possess dendrites extending millimeters away from their cell bodies (Campbell et al., 2005; Cottrell et al., 2006), with the average extending over 500 μm (Roberts et al., 2006). Interestingly, many GnRH dendrites follow routes similar to those of their axons toward the ME. Dendrites of GnRH neurons frequently initiate action potentials due to their expression of voltage-gated sodium channels (Rhodes and Llinas, 2005). As a result of the morphology of these dendrites, highly proficient action potential initiation in the distal dendrites is possible even when synaptic potentials are quite small (Witkin and Silverman, 1985; Witkin et al., 1995). Distal portions of the GnRH dendrite, for instance segments located in the arcuate nucleus of the hypothalamus (ARC), thus provide synaptic input and can potently

laboratories have found fewer than 5% of kisspeptin neurons exhibit LepRs (Donato et al., 2011; Louis et al., 2011). The latter results appear to be borne out by the lack of a reproductive phenotype in mice with a targeted deletion of LepRs from kisspeptin neurons (Donato et al., 2011). Similarly, our preliminary data suggest that insulin sensing directly by kisspeptin neurons plays a minor role in mouse fertility (Qiu et al., 2011). Thus, leptin/insulin sensing outside of the dedicated reproductive circuitry is likely to play a role in their effects on reproduction.

POMC neurons are well positioned to be a direct target of leptin and insulin signals. POMC neurons express LepRs (Cheung et al., 1997; Elmquist et al., 1998; Baskin et al., 1999) and IRs (Benoit et al., 2002). LepRs in POMC neurons mediate a portion of leptin actions on energy homeostasis, as mice lacking LepRs specifically in POMC neurons are mildly obese and hyperleptinemic (Balthasar et al., 2004). Although deletion of IRs from POMC neurons does not affect body weight (Konner et al., 2007), simultaneous deletion of IRs and LepRs from POMC neurons produces more severe insulin resistance and diabetes than deletion of each individual receptor alone (Hill et al., 2010). Therefore, POMC neurons appear to be one important site where insulin and leptin signals interact to regulate energy and glucose homeostasis.

Our recent studies also pinpointed POMC neurons as a target of leptin/insulin actions important for fertility. We have reported that female mice lacking both leptin and IRs in POMC neurons ($IR/LepR^{POMC}$) exhibit lengthened reproductive cycles, follicular arrest, hyperandrogenemia, and infertility. These mice lack IRs and LepRs in POMC-expressing cells in the hypothalamus and pituitary corticotrophs and melanotrophs, but retain them in other cell types and tissues, such as liver and ovary (Hill et al., 2010).

These results were confirmed by an absence of altered IR and LepR expre2(c)1 Tcpr an ot345 Tcypesranan4(pr)1 ar5.5(i)-.5(dual)-400-354.

Further studies are required to determine whether endorphin production in these mice is reduced, and the signaling mechanisms involved.

ESTROGENS ACT ON POMC NEURONS TO REGULATE BOTH REPRODUCTION AND ENERGY HOMEOSTASIS

Steroid hormones such as E_2 exert potent feedback at both the neural and pituitary levels to regulate the HPG axis. During much of the female reproductive cycle, E_2 reduces the GnRH pulse amplitude (Sarkar and Fink, 1980; Caraty et al., 1989; Chongthammakun and Terasawa, 1995; Evans et al., 1994) and inhibits LH release via negative feedback actions on the hypothalamus as well as the pituitary gonadotropes (Shupnik et al., 1988; Shupnik, 1996). A similar mechanism appears to be at work in males via aromatization of testosterone to E_2 (Veldhuis and Dufau, 1987; Finkelstein et al., 1991a; b; Bagatell et al., 1994; Hayes et al., 2000; Schnorr et al., 2001). In the course of the later stage of the follicular phase, circulating E_2 levels rise resulting in a biphasic effect on GnRH secretion, causing a noticeable suppression of pulsatile GnRH and LH secretion, followed by an induction of a high amplitude GnRH surge supplementary to the LH surge, a process termed positive feedback (Crowder and Nett, 1984; Moenter et al., 1990). Lesion studies performed in the rat and hamster (Brander and Barraclough, 1980; Wiegand et al., 1980) have implicated anatomically distinct brain regions for the conveyance of the positive and negative feedback. These studies localized negative feedback to the ARC and ME and positive feedback to the POA and the suprachiasmatic nucleus.

Both positive and negative feedback regulation are primarily mediated by ER, but not by estrogen receptor-(ER). This is demonstrated by observations that global deletion of ER mice abolishes the positive and negative feedback responses, while mice with global ER de“ciency appear to retain normal feedback responses (Couse et al., 1995, 2003; Wintermantel et al., 2006). However, the sites where estrogens act to regulate the HPG axis have not been fully revealed. Wintermantel et al. (2006) demon-

(VMH) may serve as an important connection point relaying metabolic and reproductive cues.

The physiological relevance of VMH neurons to the regulation of body weight homeostasis is well recognized. Ikeda et al. (1995) discovered that a transcription factor, SF1, is expressed exclusively in the VMH neurons within the brain. SF1 neurons constitute the majority of VMH neurons (Stallings et al., 2002). During early development, SF1 is essential for the formation of the VMH architecture, as mice with embryonic deletion of SF1 gene do not form a VMH (Dellovade et al., 2000). These SF1 knockout mice develop massive obesity (Majdic et al., 2002). It is important to note that

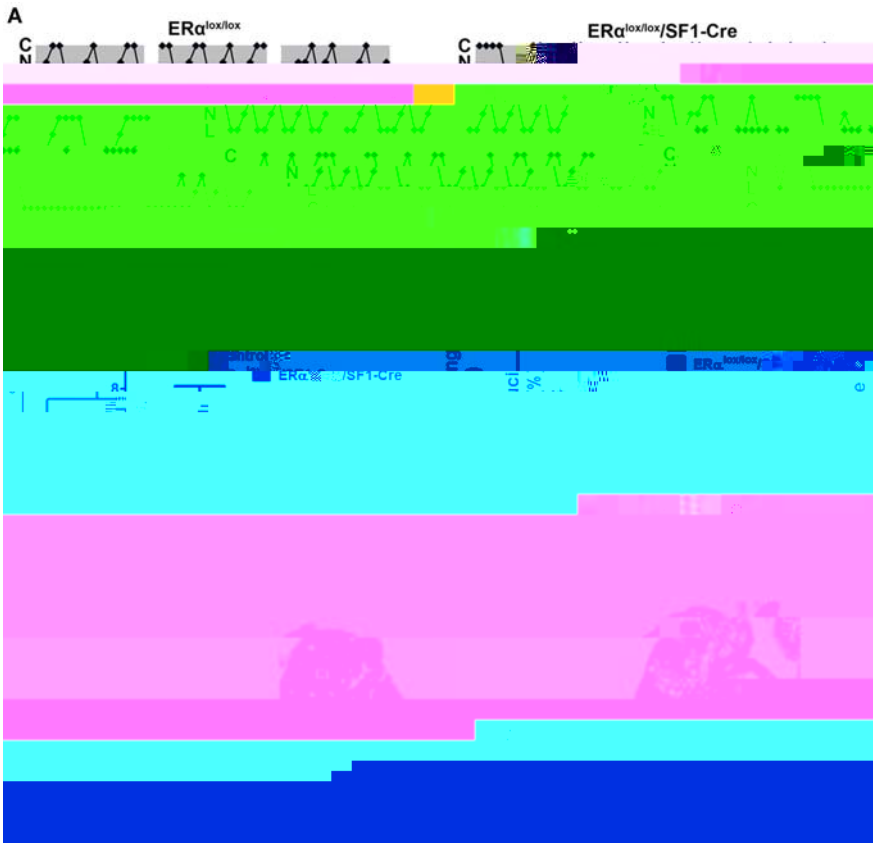

FIGURE 2 | Reproductive phenotype of female mice lacking ER in SF1 neurons (ER lox/lox /SF1…Cre). (A) Estrus cycles from 12-week-old female

E. B., Kuijper, J. L., Clifton, D. K., and Steiner, R. A. (1996). Leptin is a metabolic signal to the reproductive system. *Endocrinology* **137**, 3144…3147.

Baskin, D. G., Breininger, J. F., and Schwartz, M. W. (1999). Leptin receptor mRNA identi“es a subpopulation of neuropeptide Y neurons activated by fasting in rat hypothalamus. *Diabetes* **48**, 828…833.

Benoit, S. C., Air, E. L., Coolen, L. M., Strauss, R., Jackman, A., Clegg, D. J., Seeley, R. J., and Woods, S. C. (2002). The catabolic action of insulin in the brain is mediated by melanocortins. *J. Neurosci.* **22**, 9048…9052.

Blaustein, J. D., and Feder, H. H. (1980). Nuclear progestin receptors in guinea pig brain measured by an in vitro exchange assay after hormonal treatments that affect lordosis. *Endocrinology* **106**, 1061…1069.

Blaustein, J. D., and Wade, G. N. (1976). Ovarian in”uences on the meal patterns of female rats. *Physiol. Behav.* **17**, 201…208.

Boehm, U., Zou, Z., and Buck, L. B. (2005). Feedback loops link odor and pheromone signaling with reproduction. *Cell* **123**, 683…695.

Broberger, C., Johansen, J., Johansson, C., Schalling, M., and Hökfelt, T. (1998). The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc. Natl. Acad. Sci. U.S.A.* **95**, 15043…15048.

Bruni, J. F., Van Vugt, D., Marshall, S., and Meites, J. (1977). Effects of naloxone, morphine and methionine enkephalin on serum prolactin,

system. J. Chem. Neuroanat. 36, 131…137.
DeFazio, R. A., Heger, S., Ojeda, S. R., and Moenter, S. M. (2002). Activation of A-type gamma-aminobutyric acid receptors excites gonadotropin-releasing hormone neurons. Mol. Endocrinol. 16, 2872…2891.
Dellovade, T. L., Young, M., Ross, E. P., Henderson, R., Caron, K., Parker, K., and Tobet, S. A. (2000). Disruption of the gene encoding SF-1 alters the distribution of hypothalamic neuronal phenotypes. J. Comp. Neurol. 423, 579…589.
Dhillon, H., Zigman, J. M., Ye, C., Lee, C. E., McGovern, R. A., Tang, V., Kenny, C. D., Christiansen, L. M., White, R. D., Edelstein, E. A., Coppari, R., Balthasar, N., Cowley, M. A., Chua, S. Jr., Elmquist, J. K., and Lowell, B. B. (2006). Leptin directly activates SF1 neurons in the VMH, and this action by leptin is required for normal body-weight homeostasis. Neuron 49, 191…203.
Divall, S. A., Williams, T. R., Carver, S. E., Koch, L., Brüning, J. C., Kahn, C. R., Wondisford, F., Radovick, S., and Wolfe, A. (2010). Divergent roles of growth factors in the GnRH regulation of puberty in mice. J. Clin. Invest.