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Gq-mER signaling has opposite effects on hypothalamic orexigenic and anorexigenic neurons

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Abstract

Two populations of cells within the hypothalamus exert opposite actions on food intake: proopiomelanocortin (POMC) neurons decrease it, while neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons increase it. 17 β -Estradiol (E2) is a potent anorexigenic hormone that exerts both genomic and non-genomic, rapid actions on these metabolic neurons. This review focuses on the rapid membrane effects of E2 in both POMC and NPY/AgRP neurons and how these combined effects mediate the anorexigenic effects of this steroid.

Keywords

17 β -estradiol; NPY/AgRP; POMC; energy homeostasis

I. E2 feedback and control of non-reproductive homeostatic functions

Besides its quintessential role in the feedback control of the reproductive axis, E2 modulates a number of hypothalamic-regulated autonomic functions, most notably energy homeostasis and temperature. E2 signaling via ER α is a critical component in the hypothalamic regulation of energy balance [1]. In rodents, hypo-estrogenic states are clearly associated with decreased activity and an increase in body weight [2,3,4,5,6,7,8,9,10]. In humans, a loss-of-function mutation in ER α has a clear metabolic phenotype in man with expression of type 2 diabetes, hyperinsulinemia and obesity [11]. However, global reinstatement of an ER α that is lacking the ERE targeting domain is sufficient for “rescuing” the metabolic deficits in mice [12]. These findings suggest an important role for non-ERE mediated E2 signaling. Moreover, brain-specific knockout of ER α causes hyperphagia and hypometabolism [13,14], and selective knockdown of ER α in proopiomelanocortin (POMC) neurons appears to recapitulate the hyperphagic phenotype in female mice [14]. However, there are at least two caveats that impact the interpretation of gene deletion experiments. Firstly, ER α is a transcription factor affecting the expression of hundreds of genes important for cell signaling, and many of these genes are essential for mER initiated responses that

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contribute to POMC excitability and hence control of energy homeostasis [15,16]. Secondly, POMC-Cre (mice utilized in [14]) is also expressed in progenitor neurons that are destined to become neuropeptide Y (NPY) neurons and perhaps other hypothalamic and extrahypothalamic neurons [17,18]. Therefore, ER α knockout spreads well beyond the single neuron phenotype as originally proposed. Hence, one must be cautious in interpreting ER α knockout (global or targeted) experiments.

Experiments dating back three decades determined that the anorectic effects of E2 in rodents are mediated through CNS sites of action since direct injections of E2 into the paraventricular nucleus of the hypothalamus or arcuate/ventromedial nucleus are effective to reduce food intake, body weight and increase wheel running activity in females [19,20,3]. This is due, in part, to the actions of E2 on arcuate POMC and NPY neurons [21], which optogenetic and ablation studies have definitively proven essential in suppressing or enhancing food intake, respectively [22,23,24]. A number of experiments have shown that E2 up-regulates the expression of the peptide β -endorphin in POMC neurons in ovariectomized female guinea pigs and increases the mRNA expression of POMC in both mice and guinea pigs [25,26,27,28]. Furthermore, there is a decrease in hypothalamic POMC mRNA levels in postmenopausal women [29]. In addition, E2 reverses the ovariectomy-induced increase in arcuate NPY protein and mRNA expression in rodents [30,31,27]. Therefore, it appears that the arcuate nucleus and particularly POMC and NPY neurons are major targets for the anorectic actions of estrogen, which underscores their importance in the control of energy homeostasis. In addition, POMC neurons are critical for the regulation of feeding behavior and are also involved in the rewarding aspects of food intake [32,33].

II. Discovery of a Gq-mER signaling pathway in POMC neurons—the “yin”

Over the past two decades, substantial evidence has been generated in the support of a novel G α_q -coupled membrane ER (G α_q -mER). Intracellular sharp electrode and whole cell patch recording from guinea pig and mouse hypothalamic slices have been used to characterize this G α_q -mER [34,35,8]. These hypothalamic slice studies established that E2 acts rapidly and stereospecifically within physiologically-relevant concentrations ($EC_{50} = 7.5$ nM) to significantly reduce the potency of μ -opioid and GABA $_B$ agonists (i.e., desensitize) to activate an G protein-coupled inwardly rectifying K $^+$ channels (GIRKS) in POMC neurons [34,35]. In these anorexigenic neurons, estrogenic desensitization of μ -opioid and GABA $_B$ receptors is mimicked either by stimulation of adenylyl cyclase with forskolin or by direct protein kinase A (PKA) activation with the non-hydrolyzable cAMP analog Sp-cAMP, in a concentration-dependent manner [34,35]. Furthermore, the selective PKA antagonists KT5720 and Rp-cAMP block the effects of E2. As one would predict from the extensive literature on desensitization of GPCRs [36], PKA is downstream in a signaling cascade that is initiated by a G α_q -coupled membrane ER that is linked to activation of phospholipase C (PLC)-protein kinase C (PKC)-PKA [35,8]. E2 does not alter the affinity of the μ -opioid and GABA $_B$ receptors for their respective receptors [37]. Furthermore, the ER antagonists ICI 164,384 and ICI 182,780 block the actions of E2 with subnanomolar affinity ($K_i = 0.5$ nM) that is similar to K_i for antagonism of ER α [38,34]. These pharmacological findings clearly argue for a novel G-protein-coupled membrane receptor with high selectivity for E2.

About a decade ago a diphenylacrylamide compound, STX, that does not bind ER α or ER β [35,8] was developed to selectively target the G α_q -mER and its downstream signaling cascade --phospholipase C β -protein kinase C δ -protein kinase A pathway-- that mediates μ -opioid and GABA $_B$ desensitization in hypothalamic neurons. The design arose out of studies in which we found that E2 stereospecifically (17 α -estradiol is not active) activates the G α_q -mER signaling pathway (see above), and these actions were blocked by the ER antagonist

ICI 182,780 [34,35,8]. The results from these physiological and pharmacological experiments led to the design of STX, which is structurally similar to 4-OH tamoxifen, to target the Gαq-mER signaling pathway [35]. Most importantly, both STX and E2 activated this Gαq signaling pathway in POMC neurons from mice lacking both ERα and ERβ and in GPR30-knockout mice [8,39]. However, definitive characterization (i.e., cloning) of this novel Gαq-mER is currently a work in progress.

III. Discovery of a Gq-mER signaling pathway in NPY/AgRP neurons—the “yang”

We have recently shown that a functionally complementary Gq-mER pathway is present in NPY/AgRP neurons [40]. In contrast to POMC cells, the Gq-mER ligand STX rapidly enhances the ability of GABA_B receptors to activate GIRKS, and co-administering the estrogen receptor antagonist ICI 182,780 inhibits such effects. Interestingly, NPY/AgRP cells also apparently possess a rapid ERα signaling component [40]: activating ERα with PPT in NPY neurons rapidly causes effects opposite to those of the Gq-mER, suppressing the ability of GABA_B receptors to activate GIRKS. In gonadectomized mice, administering the “nonselective” E2 either enhances or suppresses GABA_B-mediated currents in different NPY/AgRP neurons [40]. Co-administering PI3 Kinase inhibitor, specifically a selective inhibitor of p110beta, results in E2 only enhancing the GABA_B mediated response. Therefore, ERα appears to be coupled via PI3K to inhibition of the GABA_B response in NPY/AgRP neurons. Thus, one hypothesis is that the effects of E2 depend on the relative expression of ERα vs. Gq-mER in these orexigenic cells (Figure 1). When Gq-mER expression predominates, the NPY/AgRP cell may serve a metabolic function, while those cells expressing relatively more ERα help regulate reproduction.

IV. Gq-mER and control of energy homeostasis

The ability of STX to mimic the selective actions of E2 on POMC and NPY/AgRP neuronal activity bolstered our hypothesis that the Gαq-mER may have a role in the control of energy homeostasis. Indeed, in translational animal experiments we have demonstrated that peripheral administration of STX mimics the effects of E2 in controlling energy homeostasis [8,28,41]. As predicted from the complementary effects of STX on membrane excitability in POMC and NPY/AgRP neurons, both E2 and STX reduce food intake and, subsequently, the post-ovariectomy body weight gain. STX and E2 inhibit food intake in ovariectomized guinea pigs by reducing meal frequency, and there is a subsequent reduction in abdominal fat accumulation [41]. In support of a hypothalamic site of action, treatment with STX, similar to E2, induces new gene transcription in the arcuate nucleus [28]. Many of the regulated genes in the arcuate nucleus are involved in the control of neuronal excitability (e.g., Cav3.1) and intracellular signaling in hypothalamic neurons [28]. For example, the PI3 kinase regulatory subunits are regulated by E2 and STX: PI3 kinase p55 mRNA is increased by E2 treatment [42] and PI3 kinase p85α mRNA is upregulated by STX [28]. Therefore, Gαq-mER appears to function in the estrogenic control of energy homeostasis in the arcuate nucleus.

V. Gq-mER and regulation of core body temperature

Another critical homeostatic function modulated by circulating estrogens is the maintenance of core body temperature (T_c). In fact, hot flashes affect 75–85% of perimenopausal and postmenopausal women [43]. Hot flashes are characterized by periods of sweating and peripheral vasodilation and are often associated with increased environmental temperature [44]. Therefore, a hot flash can be defined as an exaggerated heat dissipation response initiated by the preoptic temperature sensitive neurons. Although the mechanism behind this

response is not known, repeated observations have found that the majority of hot flashes are preceded by elevation in Tc independent of peripheral vasoconstriction or elevated metabolic rate [45,46]. Therefore, it has been postulated that elevated Tc may serve as one trigger of menopausal hot flashes [47,44]. In general, there is compelling experimental evidence that the incidence of hot flashes in hypo-estrogenic females is decreased by E2 treatment [48,49,47]. The estrogenic reduction in the naloxone-induced rise in tail skin temperature of morphine-dependent ovariectomized rats has been the industry standard for a hot flash model [50,51,52]. The morphine-dependence, naloxone-precipitated withdrawal rat model has a number of drawbacks because of the adverse autonomic reactions independent of an elevation in core and skin temperature. But the model does highlight the involvement of CNS opioid effects (e.g., from POMC neurons) directly or indirectly on preoptic temperature sensitive neurons [53].

We established a guinea pig “hot flash” model based on the hypothesis that the expression of vasomotor symptoms in menopausal women is due to the reduced thermo-neutral zone in core body temperature [46]. In the ovariectomized female guinea pig, both E2 and STX significantly reduce Tc compared to animals receiving vehicle injections [41]. The exact cellular target for E2 and specifically the Gαq-mER modulation of Tc has not been identified. However, one potential cellular mechanism is the direct action of E2 via the Gαq-mER on thermosensitive (GABAergic) neurons in the medial preoptic area of the hypothalamus [54,55,56]. Previous studies in ovariectomized female guinea pigs have shown that medial preoptic GABAergic neurons respond to acute E2 treatment via the Gαq-mER signaling pathway to attenuate GABA_B inhibitory input, leading to increased GABA neuronal activity [57]. Moreover, activation of medial preoptic GABA neurons are responsible for evoking the vasomotor responses in rodents [58] underlying heat dissipation responses (i.e., vasodilatation, sweating) seen in women experiencing hot flashes.

Importantly, the coupling of Gαq-mER to downstream signaling pathways is similar to the serotonin 5HT_{2A/2C} receptors, which when activated, lower Tc and are implicated in thermoregulation dysfunction caused by ovariectomy [59,60]. Selective serotonin reuptake inhibitors elevate endogenous serotonin levels and are therefore efficacious for treating hot flashes [61] and can significantly attenuate the effects of ovariectomy on thermoregulation in rodents [62]. Moreover, both the Gαq-mER and 5HT_{2C} receptors increase POMC neuronal excitability [63]. These similarities imply that serotonin via its Gαq-coupled receptor and E2 via Gαq-mER have similar cellular targets in the hypothalamic neurons that regulate Tc and energy homeostasis.

VI. Summary

It is obvious from the plethora of studies using membrane-delimited E2 ligands and the Gq-mER selective ligand STX that “genomic” actions of E2 in the brain do not require the direct nuclear targeting of estrogen receptors (ER α and ER β). Signals that are initiated by E2 at the plasma membrane can trigger multiple intracellular signaling cascades including activation of MAPK, PI3K, and PKC pathways [64,65,66,67,68] that result in the phosphorylation of hundreds of proteins that ultimately can affect cell excitability and gene transcription. E2 can bind to the novel Gαq-mER to upregulate cAMP in POMC neurons by increasing adenylyl cyclase activity within minutes [34]. Cyclic-AMP activates PKA, which in turn phosphorylates K⁺ channels [69] and/or calcium channels to [70] to alter their activity. In addition, PKA can phosphorylate CREB to elicit new gene transcription [71,72,73,74]. Alternately, the Gq-mER in NPY/AgRP neurons elicits rapid effects on K⁺ channels opposite to those seen in POMC cells (Figure 1). Therefore, not only does membrane excitability change within a matter of seconds, but gene transcription can be activated within a relatively short time course (within tens of minutes) in neurons

independent of classic estrogen receptors (ER α and ER β) interacting with EREs. Thus, we need to elucidate the role of membrane estrogen receptors not only in hypothalamic functions but also in higher cortical functions. By developing selective non-steroidal agonists for targeting mERs we will be able to treat menopausal symptoms without the concern for the deleterious reproductive and cardiovascular effects of estrogens.

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Highlights

- 17 β -estradiol (E2) rapidly controls membrane excitability through non-genomic mechanisms in hypothalamic neurons that control feeding.
- E2 decreases GABAergic inhibition on POMC cells, which are anorexigenic, via a Gq-coupled membrane estrogen receptor (Gq-mER).
- E2 decreases or increases GABAergic inhibition of orexigenic NPY/AgRP neurons depending on whether it binds to ER α or Gq-mER, respectively.
- The Gq-mER also plays a role in thermoregulation in mammals.

Figure 1.

Schematic representation showing how E2 may inhibit or excite NPYAgRP and POMC neurons in the hypothalamus. Abbreviations: Gq-mER, Gq-coupled membrane estrogen receptor; GIRK, G protein-coupled inwardly rectifying potassium channel; ER α , estrogen receptor α ; NPY/AgRP, neuropeptide Y/Agouti-related peptide; POMC, proopiomelanocortin