Focus Article

mGlu receptors in endocrine organs

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Metabotropic glutamate (mGlu) receptors in the central nervous system are known to be essential for neuroplasticity associated with normal brain functions and are also critically involved in various neurological and psychiatric disorders. A recent surge of publications supports the presence, importance, and functionality of mGlu receptors outside the central nervous system with a unique distribution within various tissues. Group I, II, and III mGlu receptors are found in a wide range of peripheral organs including parts of the peripheral nervous system and nonneural organs such as hypophysis, pancreas, adrenal medulla, and the reproductive system. The distinct distribution of mGlu receptors in peripheral tissues is discussed in terms of possible functional endocrine implications.

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INTRODUCTION

Besides its role as an excitatory neurotransmitter, glutamate has been extensively studied as a modulator of endocrine and neuroendocrine events. Several, if not all, pituitary hormones are under the control of glutamatergic input, acting at ionotropic (iGlu) and/or metabotropic glutamate (mGlu) receptors. Even though the ionotropic component of glutamate response has the largest influence on endocrine regulation, mGlu receptor activation can fine tune synaptic transmission and alter responsiveness of neurons involved in endocrine modulation. mGlu receptors have also been found on cell types peripheral to the CNS including osteoblasts, hepatocytes, pancreatic cells, and endothelial cells, among others.

ACTIONS OF mGlu RECEPTOR ACTIVATION ON HYPOTHALAMIC FACTORS

Glutamate acts on endocrine function mostly by modulating hypothalamic activity which in turn alters hormone release. mGlu receptors have been found not only in different regions within the hypothalamus but also in the three lobes of the pituitary gland. They are most densely expressed in hypothalamic areas associated with neuroendocrine regulation such as the supraoptic (SON), arcuate (ARC), paraventricular (PVN), and ventromedial (VMN) nuclei, and the preoptic area (POA).[1]

Evidence from our laboratory indicates that, in rats, glutamate-induced release of substance P in the ARC and median eminence (ME) is mediated by activation of N-Methyl-D-aspartate (NMDA) and Group I mGlu receptors.[2] This increase may mediate, at least in part, the stimulatory effect of glutamate on luteinizing hormone (LH) and prolactin (PRL) secretion. In contrast, the 2-amino-3-(5-methyl-3-oxo-1,2-oxasol-4-yl)propanoic acid (AMPA)/ kainate (KA) receptors and Group II and III mGlu receptors do not appear to contribute to substance P release.[2]

On the other hand, both Group I and II mGlu receptors' activation decreases α-melanocyte stimulating hormone (MSH) release from hypothalamic fragments.[3] However, mGlu receptor activation does not affect the release of this peptide from the posterior pituitary in male rats.[3] Since α-MSH inhibits the preovulatory PRL and LH surge and ovulation of female rats,[4] mGlu receptor activity at α-MSH level could lead to increased LH production.

Whereas administration of iGlu receptor agonists stimulates gonadotropin-releasing hormone (GnRH) and LH release,[5] agonists for Group I and II mGlu receptors produced no change in hypothalamic GnRH release and LH secretion *in vitro*.[6] However, a

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subpopulation of GnRH neurons recently detected in the medial septum was excited by Group I mGlu receptor agonists.[7] The increase of hypothalamic stimulatory factors such as oxytocin and substance P release induced by Group I mGlu receptor agonists may also contribute to stimulatory action of glutamate on LH release. On the other hand, since the activation of presynaptic Group II/III mGlu receptors inhibits gamma-aminobutyric acid (GABA)-ergic input to GnRH neurons, mGlu receptors could reduce GnRH release via GABA modulation.[8] Group I mGlu receptors have also been implicated in prostaglandin E(2)-mediated masculinization of adult sex behavior in rats in response to the surge in serum testosterone at birth.[9]

The mGlu receptors' system appears to play a crucial role in mediating neuroendocrine responses to stress. Aminocyclopentane-1,3-dicarboxylic acid (ACPD), a nonselective mGlu receptor agonist, induced a significant increase in plasma corticosterone following intracerebroventricular (i.c.v) administration.[10] Other authors also reported involvement of Group I mGlu receptors in stimulation of the hypothalamic–pituitary–adrenal (HPA) axis.[11,12] Also, a Group II mGlu receptor antagonist increased plasma corticosterone and corticosterone-releasing factor (CRH) secretion from mice isolated hypothalami, while Group II mGlu receptor agonists induced no modification.[13] The lack of effect of Group II mGlu receptor agonists supports the hypothesis that endogenous activation of Group II mGlu receptors could tonically inhibit hypothalamic CRH release. If so, Group II mGlu receptor antagonists might become valuable tools to study the efficiency of the HPA axis under physiological and pathological conditions, e.g., in chronic stress or mood disorders. Also, i.c.v. administration of nonselective Group III mGlu receptor agonists L-(+)-2-Amino-4-phosphonobutyric acid (L-AP4) and L-Serine-O-phosphate (L-SOP) induced an increase in corticosterone levels in male rats.[11] A selective mGlu7 receptor agonist elevates the plasma stress hormones corticosterone and CRH and mGlu7–/–mice show a moderated reduction in serum levels of corticosterone and ACTH.[14,15]

MODULATION OF GROWTH HORMONE AND PROLACTIN RELEASE BY mGlu RECEPTOR ACTIVATION

A significant decrease in serum growth hormone (GH) concentrations after central (i.c.v.) administration of ACPD (a Group I and II mGlu receptor agonist) and following systemic administration of ibotenic acid (a weak agonist of all mGlu receptors) was observed in prepubertal animals.[16] We showed the presence of Group II mGlu receptor in somatotropes and have observed an apoptotic effect of (2S,1S,2S)-2-(carboxycyclopropyl)-glycine (L-CCG-I), a Group II mGlu receptor agonist, on this cell type,[17] which might account for the reported inhibition in GH production. mGlu receptor inhibitory effects contrast with potent stimulatory actions observed following iGlu receptor activation.[16]

Control of PRL production and secretion from lactotropes of anterior pituitary gland is thought to be determined primarily by levels of dopamine released from the ARC. Via D2 receptors, dopamine inhibits PRL gene expression and release,[18] and reduces lactotroph proliferation.[19] Glutamate regulates basal PRL secretion and also affects the physiological response of this hormone to stimuli such as suckling and stress. The mechanism by which glutamate affects PRL release remains unclear. It could involve mediation of PRL-releasing factors in the hypothalamus such as substance P, vasoactive intestinal peptide, oxytocin and/or inhibiting factors such as dopamine and GABA.[20,21] Group I mGlu receptor activation reduces GABA release from hypothalamus of male rats,[3] a decrease that could mediate the stimulatory action of glutamate on PRL release. Johnson and Chamberlain (2002)[22] suggested that LY379268, a Group II mGlu receptor agonist, produces disinhibition of tuberoinfundibular dopamine release by acting at presynaptic Group II mGlu receptors located on inhibitory GABAergic inputs to the ARC in rats.

Although glutamate acts mainly at the hypothalamic level, this neurotransmitter can also act on lactotropes.[6] In fact, glutamate may have a dual direct effect on PRL release from anterior pituitary cells of female rats: it exerts stimulatory action when it interacts with iGlu receptors while it has an inhibitory effect when it activates Group II mGlu receptors. Caruso et al. (2004)[17] demonstrated that Group II mGlu receptors are present in lactotropes in rat anterior pituitary, which tallies with functional data showing that L-CCG-I, a Group II mGlu receptor agonist, decreases PRL release from anterior pituitary gland.[17] On the other hand, Group I and III mGlu receptors do not appear to be involved in the regulation of PRL secretion on anterior pituitary cells. We also showed that L-CCG-I induced apoptosis in lactotropes,[17] which may account for the inhibition in PRL secretion exerted by these receptors.

Interestingly, we observed that Group II mGlu receptor agonists LY379268 and LY354740 may have a dopamine partial agonist action since they bind to D2 receptors in rat striatum and to human cloned D2long receptors in chinese hamster ovary (CHO) cells.[23] This binding correlates with the inhibition of

PRL release from anterior pituitary cells. Accordingly, LY379268 can reduce hyperprolactinemia under several conditions in rats.[22] It is likely that the actions of these Group II mGlu receptor agonists *in vivo* have both glutamate and dopamine components.[24,25]

LOCALIZATION OF mGlu RECEPTORS IN ENDOCRINE ORGANS

Recent studies detected mGlu receptor expression in numerous tissues under both physiological and pathological conditions. Groups I, II and III are found on cell types peripheral to CNS including pancreatic cells, hepatocytes, osteoblasts, endothelial cells, T- and B-cells, among others.

Of Group I, mGlu5 receptor has been detected in melanocytes, pinealocytes, pancreatic islets, hepatocytes, and rat testis (reviewed in Ref 26). From Group II, mGlu3 receptor has been found in hepatocytes, pinealocytes, and pancreatic islets (reviewed in Ref 26). mGlu4 and mGlu8 receptors, belonging to Group III mGlu receptors, are found in pancreatic α-cells.[27] The roles of mGlu receptors outside the CNS include regulating mineralization in the developing cartilage, modulating lymphocyte cytokine production and gastrointestinal secretory function, directing the state of differentiation in embryonic stem cells, and controlling hormone production in the adrenal gland and pancreas.[28]

As implied by the data above, mGlu receptors are involved in regulation of hormone secretion in the endocrine pancreas. Several authors have analyzed the glutamatergic system in animal models of diabetes. mGlu receptors have differential expression in brain regions of diabetic rats as a function of age.[29] In insulin-induced hypoglycemiant and diabetic rats, an upregulation of mGlu5 receptors leads to increased inositol triphosphate (IP3) content which mediates Ca^{2+} overload that causes cell damage and neurodegeneration.[30] However, endogenous activation of mGlu5 receptors is required for optimal insulin response to glucose in mice and is also involved in the correct glucagon response to insulin challenge.[31] Specific agonists for Group I and II mGlu receptors increased the release of insulin in the presence of glucose, whereas Group III agonists inhibited insulin release at high glucose concentrations.[32]

In islets of Langerhans, L-glutamate is stored in glucagon-containing secretory granules of α-cells and cosecreted with glucagon in low-glucose conditions. Glutamate triggers secretion of GABA from β-cells which in turn inhibits glucagon secretion from α-cells, although glutamate can also act autocrinally on α-cells inhibiting glucagon secretion through mGlu4 receptor activation.[33] However, Tong et al. (2002)[27] demonstrated mGlu8 receptor-dependent inhibition of glucagon release from rat pancreatic islets. i.c.v. injection of ACPD (a Group I and II mGlu receptor agonist) increases plasma glucose levels and more sustained elevations in corticosterone, epinephrine, and norepinephrine.[10]

On the other hand, immunocytochemical techniques revealed that two mGlu receptor subtypes (mGlu1a and mGlu5 receptors) are expressed in bovine chromaffin cells of the adrenal medulla and are able to stimulate release of adrenaline and noradrenaline in a dose-dependent manner.[34]

Group II (but not Group III) mGlu receptor agonists inhibit norepinephrine-stimulated melatonin synthesis and N-acetyltransferase activity, possibly involving the mGlu3 receptor subtype expressed in pineal gland from rats.[35]

mGlu2/3 receptors are heavily expressed in corpus luteum and in smooth muscle in the wall of arterioles within the stroma and the hilus of ovary in the nonhuman primate *Macaca fascicularis*. They are also found in different structures of the ovary, uterine cervix, myometrium, endometrium, and inflammatory cells in this primate.[36] In the ovary, mGlu2/3 receptors expression was found in oocyte and corpus luteum. In testes, intense mGlu2/3 receptors immunolabeling was found in the head of mature spermatids, interstitial, and myoid cells of rats,[37] suggesting that these receptors may be involved in ovulation, fertilization, and implantation of the ovum. Takarada et al. (2004)[38] also found mRNA for mGlu1 to 6 and mGlu8 receptors but not for mGlu7 receptors in rat testes. In particular, mGlu1 receptor is expressed in Sertoli cells and mGlu5 receptor in germinal cells with the exception of spermatogonia.[39] In human testes, mGlu5 receptor immunolabeling was intense inside the seminiferous tubuli, whereas mGlu1 receptor immunolabeling was detected in Leydig cells of intertubular spaces, where their activation could likely stimulate testosterone synthesis.[39]

In the rat kidney, mGlu2/3 receptors were found in granular cells of the afferent arteriole suggesting a potential role in the control of renin release.[40]

mGlu3 receptors were demonstrated to be upregulated in response to persistent hypoxic status such as fibrotic/cirrhotic conditions in the rat liver, exerting protective effects and improving hepatic function,[41] although an agonist of mGlu2/3 receptors had no effect on rat hepatocyte death induced by anoxia.[42] On the contrary, endogenous mGlu5 receptor activation is associated with liver damage induced by lipopolysaccharide and d-galactosamine[43] or by acetaminophen[44] in mice. Storto et al. (2000)[42] suggested that mGlu5

receptor activity is induced by glutamate released from rat hepatocytes exposed to anoxic conditions. In turn, selective blockade of mGlu5 receptor protects against hepatocyte death induced by hypoxia[45] and oxidative stress[44] in rodents.

In summary, this wide distribution of mGlu receptors in several endocrine organs may have important therapeutic and toxicological implications.

ESTROGEN RECEPTOR–mGlu RECEPTOR INTERACTION: A NOVEL MECHANISM MEDIATING ESTROGEN ACTION

Besides the classical, intracellular estrogen receptor (ER), it is now known that many rapid effects of estrogen are initiated by estradiol acting at the surface of plasma membrane.[46–48] Moreover, it was recently reported that membrane-localized ER can activate various mGlu receptors. Physiological (picomolar) estradiol stimulation of ERα resulted in increased cAMP response element-binding (CREB) phosphorylation through activation of mGlu1 receptors.[49] Estradiol, through both ERα and ERβ, also decreased L-type calcium channel-dependent CREB phosphorylation via activation of Group II mGlu receptors in rat striatal neurons.[50] These effects are abolished by mGlu receptor antagonists, whereas mGlu receptor agonist administration mimicks estradiol actions.[50]

Estradiol activation of mGlu receptors is independent of glutamatergic transmission.[49–51] Instead, Dewing et al. (2007)[52] proposed a transactivation mechanism by which ERs activate mGlu receptors following estradiol stimulation via direct protein–protein interaction. Caveolin proteins were found essential for various membrane ERα responses since they compartmentalize the different ERs with mGlu receptors into functional signaling microdomains.[53] In hippocampal neurons, caveolin 1 protein (CAV1) is essential for functional coupling of ERα with mGlu1 receptor. Conversely, CAV3 is necessary for ERα and ERβ activation of mGlu2/3 receptors.[54] However, interaction patterns vary with the brain region analyzed[55] and ERs can produce diverse effects through pairing with different caveolin and mGlu receptor proteins.[56]

Effects of estrogen on lordosis behavior are critically dependent on mGlu1 receptor.[52] In hypothalamic glial cells, estradiol administration results in an increase in intracellular calcium, which is believed to be critical in synthesis of neuroprogesterone and the LH surge.[57] This action is mediated by interactions between membrane ER and mGlu1a receptor.[51] Also, in hypothalamic rat astrocytes, antagonism of the mGlu1a receptor leads to a decrease in oxytocin-induced $[Ca^{2+}]_i$ response, whereas the agonist dihydroxyphenylglycine (DHPG) potentiates the oxytocin response.[51] Therefore, astrocytes will have an enhanced response to oxytocin released from magnocellular dendrites of the SON and PVN when these brain regions are simultaneously activated by glutamatergic stimulation during the milk ejection neuroendocrine reflex.

In summary, ER/mGlu receptor signaling is a potential means by which estrogens can both rapidly and persistently influence a variety of intracellular signaling processes, including neuroendocrine events.[53]

CONCLUSIONS

Available data indicate that mGlu receptor activation plays a role in the neural control of hypothalamic factors and hormone release by acting both directly on target organs or indirectly, mainly via GABAergic input modulation. On the other hand, specific mGlu receptor responses demonstrated in numerous non-neuronal peripheral tissues have proved to be relevant in the physiopathology of various endocrine systems.

Growing knowledge about mGlu receptor-mediated regulation of endocrine circuits helps us to understand multiple interactions between neural and endocrine systems. This is the case of ER–mGlu receptor physical interaction at cell membrane, which now explains several rapid and pleiotropic actions of estrogens that have baffled estrogen researchers for years. In this sense, new studies are needed to explore all known actions of estrogens and their relation to mGlu receptor transactivation. Importantly, allosteric potentiators or negative modulators of mGlu receptors developed in recent years may offer advantages over orthosteric agonists as a result of their superior selectivity.[58]

Finally, the presence of mGlu receptors in multiple endocrine organs should be considered in the development of new mGlu receptor-specific pharmacological agents for novel treatment strategies for psychiatric and neurological disorders to avoid potential side effects.

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