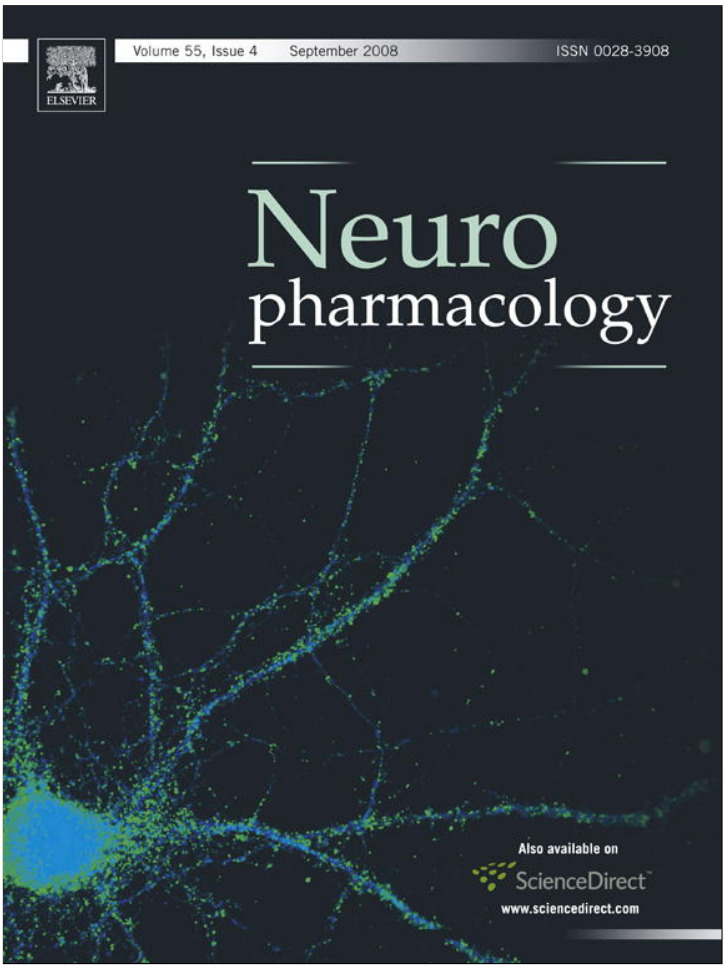

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Role of metabotropic glutamate receptors in the control of neuroendocrine function

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ABSTRACT

Glutamate exerts its effects through binding and activation of two classes of specific receptors: ionotropic (iGluRs) and metabotropic (mGluRs). Group I mGluR includes mGluR1 and mGluR5 subtypes, group II includes mGluR2 and mGluR3 subtypes and group III includes the subtypes mGluR 4, 6, 7 and 8. Glutamate and its receptors are found in all key hypothalamic areas critically involved in reproduction and neuroendocrine function. To date, considerable data support an important role for iGluRs in the control of neuroendocrine function; however, the role of mGluRs as regulators of hypothalamic-pituitary function has not been clearly elucidated.

mGluRs could be exerting a fine tune on the release of hypothalamic factors that regulate hormone release such as Substance P, GABA, alpha-MSH and CRH. Group II mGluR exert a direct inhibitory effect on anterior pituitary prolactin and GH secretion. Moreover, some group II mGluR agonists, like LY 354,740 and LY 379,268, can modulate PRL secretion from the anterior pituitary through their actions as dopamine receptor agonists. Evidence suggests a role for group III mGluR subtypes in stress-related behavioral disorders.

Several reports indicate that selective ligands for mGluR subtypes have potential for the treatment of a wide variety of neurological and psychiatric disorders, including depression, anxiety disorders, schizophrenia, epilepsy and Alzheimer's disease among others. Since converging lines of evidence suggest a role for mGluRs subtypes in neuroendocrine regulation of hormone secretion, mGluRs neuroendocrine actions must be taken in consideration to insure proper treatment of these diseases.

Moreover, discovery of selective agonists provides an opportunity to investigate the physiological role of mGluR subtypes and to directly test the neuroendocrine actions of mGluRs. Finally, mGluRs selective agonists may have an impact in the treatment of conditions involving chronic stress, such as depression and anxiety disorders, since they regulate neuroendocrine stress circuits involving the HPA axis and stress-sensitive hormones such as oxytocin and prolactin. This review aims to provide a survey of our current understanding of the effects of mGluR activation on neuroendocrine function.

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). It plays an important role in several physiological functions including learning, memory and developmental plasticity, and it has been implicated in a variety of neurodegenerative disorders (Brann and Mahesh, 1997; Dingledine et al., 1999; Riedel et al., 2003). Glutamate is also involved in critical reproductive and neuroendocrine events, such as puberty, gonadotropin pulsatility and the preovulatory gonadotropin surge and reproductive behavior (Dhandapani and Brann, 2000; Brann and Mahesh, 1994). Hence, a deficit in the glutamatergic system may also participate in the reproductive decline associated with aging (Dhandapani and Brann, 2000).

1. Glutamate receptor types

Glutamate exerts its effects through binding and activation of two classes of specific receptors: ionotropic (iGluRs) and metabotropic (mGluRs).

iGluRs form specific cationic channels while mGluRs are G-protein coupled receptors linked to various intracellular second messenger cascades. iGluRs are further classified into *N*-methyl-D-aspartate (NMDA), kainate (KA) and alpha-amino-5-methyl-3-hydroxy-4-isoxazole propionic acid (AMPA) receptors, according to their specific agonists. On the other hand, mGluRs are members of the family 3 of the G-protein coupled receptor superfamily (De Blasi

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et al., 2001). These receptors mediate slow responses by coupling to different second messenger cascades via heterotrimeric G-proteins. mGluRs are distributed in glutamatergic and non-glutamatergic neurons and have evolved as modulatory mechanisms to control excitability in the CNS (Schoepp, 2001). They can affect action potential generation in the somato-dendritic region, fine tune synaptic transmission at presynaptic terminals, and/or alter the responsiveness of the postsynaptic cell (Chu and Moenter, 2005).

mGluRs are classified into three groups according to similarities in second messenger coupling systems, molecular structure, sequence homology and their pharmacology. Group I mGluRs (mGluR 1 and 5 and their splice variants) are positively linked to phospholipase C and their activation results in increased phosphoinositide turnover (Cartmell and Schoepp, 2000). These receptors are localized in the periphery of postsynaptic densities and participate in the regulation of synaptic plasticity (Schoepp, 2001; Cartmell and Schoepp, 2000). Their interactions with ionotropic receptors or other ionic channels lead to an increase in cellular excitability; and different studies suggest that their activation facilitates glutamate release (Schoepp, 2001; Cartmell and Schoepp, 2000).

Group II (mGluRs 2 and 3) and III mGluRs (mGluRs 4, 6, 7 and 8, including splice variants) are negatively coupled to adenylate cyclase and, upon activation, inhibit cAMP production (Cartmell and Schoepp, 2000). mGluRs 2 are localized predominantly in presynaptic terminals of glutamate neurons, where they inhibit the release of glutamate and consequently maintain glutamatergic neurotransmission within physiological levels (Schoepp, 2001). On the other hand, mGluRs 3 are mainly found on the postsynaptic neuronal terminal and in glial cells (Riedel et al., 2003; Schoepp, 2001). Group III mGluRs are mainly located in or near presynaptic active zones, except for mGluR6, which is expressed in retina but is not found at significant levels in the CNS (Schoepp, 2001; Cartmell and Schoepp, 2000).

2. Localization of mGluR in neuroendocrine tissues

Both glutamate and its receptors are localized in a variety of hypothalamic nuclei which are considered to be critical for reproduction and neuroendocrine function. For example, glutamate has been localized in magnocellular and parvocellular neurons in the paraventricular nucleus (PVN), in the ventromedial (VMN), arcuate (ARC) and supraoptic (SON) nuclei, in the median eminence (ME) and the infundibular stalk (Brann and Mahesh, 1997; Goldsmith et al., 1994; Meeker et al., 1993; Van den Pol et al., 1990; Van den Pol, 1991; Thind and Goldsmith, 1995). While it is present at high concentrations in the presynaptic neuronal terminals, its levels are low in astrocytic processes (Van den Pol, 1991). In the pituitary, it has been detected in pituicytes and in axonic terminals of the posterior lobe (Meeker et al., 1991).

mGluRs have been found in different regions within the hypothalamus and in the three lobes of the pituitary gland. They are most densely expressed in hypothalamic areas associated with neuroendocrine regulation such as the SON, ARC, PVN, VMN and the preoptic area (POA) (Meeker et al., 1994).

The widespread localization of glutamate receptors in areas that are crucial for reproductive processes and neuroendocrine function indicates that this neurotransmitter plays a major role in the regulation of these events. The initial demonstration of a role for glutamate on neuroendocrine regulation was obtained after observation that neonatal administration of monosodium glutamate was followed by brain lesions and obesity (Olney, 1969). Different studies indicate that glutamate induces the secretion of several pituitary hormones *in vivo*, such as LH, PRL and GH (Terry et al., 1981; Mason et al., 1983; Brann, 1995) through binding of its receptors in the hypothalamus and the pituitary gland.

To date, considerable evidence supports an important role for iGluRs in the control of neuroendocrine function; however, the role of mGluRs as regulators of hypothalamic-pituitary function has remained largely ignored.

This review discusses the effects of the activation of selective mGluRs subtypes on the release of hypothalamic factors that regulate hormone secretion and the direct effects of mGluRs agonists on anterior pituitary hormone secretion.

3. mGluR regulation of hypothalamic GABA release

The tubero-infundibular and tuberohypophysiary GABAergic systems are involved in the regulation of anterior pituitary hormone secretion. Neuronal terminals release GABA in the ME or the posterior pituitary, and this neurotransmitter reaches the anterior pituitary through the long and short portal vessels (Duvilanski et al., 1987; Tappaz et al., 1986). GABA released in the ARC inhibits dopamine release, the major hypothalamic prolactin inhibitory factor (Tappaz, 1984; Wagner et al., 1994).

mGluRs, acting presynaptically reduce transmission at glutamatergic and GABAergic synapses (Schoepp and Conn, 1993; Chu and Hablitz, 1998). Thus mGluR-mediated presynaptic modulation of GABA release may be a mechanism for enhancing cell excitability. However, the overall effects would depend on which circuits are affected by these inhibitory interneurons.

It has been reported a specific role for both group II and III mGluRs in suppression of GABAergic transmission in the accessory olfactory bulb, primary cortical cultures and striatal cultures (Hayashi et al., 1993; Schaffhauser et al., 1998; Lafon-Cazal et al., 1999). We found that group I mGluR activation reduces GABA release from the hypothalamus and posterior pituitaries of male rats. However, this inhibitory effect on hypothalamic GABA release was not completely reversed by the specific antagonist AIDA (Pampillo et al., 2002a). Since AIDA acts preferentially at mGluR1 (Moroni et al., 1997), its inability to fully block the inhibitory effect of the group I mGluR agonist could be attributed to high mGluR5 expression in the hypothalamus, particularly in astrocytes. Astrocytes appear to play a dynamic role in regulating GABA transmission (Steinhauser and Gallo, 1996), so they could participate in the response of the GABAergic system to group I mGluR activation.

The regulation of GABA release by mGluR activation would certainly have an impact on the activity of hormonal systems modulated by GABA, such as GnRH (Dziedzic et al., 2003). Group II/III mGluRs agonists inhibit GABAergic inputs to GnRH neurons (Chu and Moenter, 2005). Since GnRH neurons are depolarized by $GABA_A$ receptor activation, this results in a decrease of GnRH release (Chu and Moenter, 2005). Although the consequence of $GABA_A$ receptor activation in GnRH neurons remains controversial (Sim et al., 2000; Sullivan and Moenter, 2005) mechanisms regulating this key synaptic input are poised to play a major role in central regulation of fertility (Bilger et al., 2001).

4. mGluR regulation of hypothalamic dopamine release

Hypothalamic dopaminergic neurons form three functionally independent and morphologically distinct systems: the periventriculohypophysial dopaminergic (PHDA) system that terminates in the intermediate lobe of the pituitary gland, the tuberohypophysial dopaminergic (THDA) system, that terminates in both the neural and the intermediate lobe of the pituitary gland, and the tuberoinfundibular dopaminergic (TIDA) system, located in the arcuate nucleus and well accepted as a major tonic regulator of adenohypophysial prolactin secretion (reviewed in Freeman et al., 2000).

Using *in vitro* and *in vivo* techniques, various studies have indicated that glutamate, acting through iGluRs, play an important role in regulating dopamine release in the brain (reviewed in

Whitton, 1997). We showed that NMDA decreased dopamine release from the hypothalamus and from the intermediate and neural lobe of the pituitary gland (Lomniczi et al., 2000; Pampillo et al., 2002c).

Evidence suggests that tubero-infundibular DA release is under the control from GABAergic input and alterations in this system can alter the levels of circulating prolactin. It has been found repeatedly that activation of group II mGluRs results in decreases in not only glutamate but also GABA release in microdialysis and *in vitro* slice release studies in several brain nuclei (for review see Cartmell and Schoepp, 2000). In addition, Johnson and Chamberlain (2002) suggested that LY 379,268, a group II mGluR agonist, produces a disinhibition of tubero-infundibular DA release by acting at presynaptic group II mGluRs located on inhibitory GABAergic inputs to the ARC. Thus, a common feature of group II mGluRs appears to be their action as presynaptic neurotransmitter release inhibitors.

We observed that group II mGluR agonists LY 379,268 and LY 354,740 may have a dopamine partial agonist action, since they bind to D_2 receptors in rat striatum and to human cloned D2Long receptors in CHO cells (Seeman et al., 2008). It is likely that the actions of these group II mGluR agonists *in vivo* (Cartmell et al., 2000; Schoepp et al., 1998) have both glutamate and dopamine components of action. For example, the enhacement by LY 354,740 of amphetamine-induced release of dopamine (van Berckel et al., 2006) may result not only from group II mGluR stimulation but also from presynaptic D_2 receptor inhibition by LY 354,740. In summary, group II mGluR agonists appear to modulate dopamine release from the hypothalamus indirectly via inhibition of GABAergic interneurons and may be acting as partial D_2 agonists. Further investigations are required to clarify this issue.

5. mGluR regulation of hypothalamic substance P release

The tachykinins, substance P (SP), neurokinin A, and neurokinin B are hypothalamic neuropeptides exerting a wide range of physiological functions (Ljungdahl et al., 1978). A large body of evidence indicates the presence of tachykinins in hypothalamic structures related to the neuroendocrine function. Different studies have implicated SP in the control of luteinizing hormone (LH) and prolactin secretion. SP has been shown to stimulate prolactin and LH secretion (Debeljuk and Lasaga, 1999) and synergistically enhance GnRH-evoked LH release from cultured pituitary cells (Hidalgo-Diaz et al., 1998).

Evidence from our laboratory indicates that glutamate-induced release of SP in the ARC and ME is mediated via activation of NMDA and group I mGluRs (Caruso et al., 2006). This increase may mediate, at least in part, the stimulatory effect of glutamate on LH and prolactin secretion. In contrast, the AMPA/KA receptors and group II and III mGluRs do not appear to contribute to SP release (Caruso et al., 2006).

6. Effect of mGluRs on alpha-melanocyte stimulating hormone release

Alpha-melanocyte stimulating hormone, α-MSH, is a tridecapeptide that belongs to the group of melanocortins and derives from the N-terminal region of the precursor peptide pro-opiomelanocortin (POMC). Melanocortins have a broad range of physiological actions, such as an influence on energy homeostasis, neuroendocrine regulation of sexual behavior and endocrine glands, regulation of the HPA axis and the cardiovascular system, etc. Melanocortins exert their effects through binding to G-protein coupled receptors (MC1-R to MC5-R). MC3-R and MC4-R have high levels of expression in brain, and they can both be activated by α-MSH. MC4-R has generated wide interest for its involvement in obesity (Huszar et al., 1997). Melanocortins are expressed in a variety of tissues but mainly in the pituitary gland and in the CNS where melanocortin-expressing neurons are found in the ARC and in the nucleus of the solitary tract in the brain stem (Eberle, 1988).

Glutamate affects the release of α-MSH in the hypothalamus. Superfusion of rat hypothalamic slices with NMDA increased α-MSH release, and this effect was mediated by nitric oxide (NO) (Wayman et al., 1994). On the other hand, both group I and II mGluR activation decreased α-MSH release from hypothalamic fragments (Pampillo et al., 2002a). Since α-MSH is also synthesized in melanotropes in the posterior pituitary, where both glutamate and its receptors have been localized, glutamate could also influence α-MSH secretion at this level. However, mGluR activation does not affect the release of this peptide from the posterior pituitary in male rats (Pampillo et al., 2002a) and glutamate increases intracellular calcium concentration in melanotropes through the activation of ionotropic but not metabotropic receptors (Giovannucci and Stuenkel, 1995).

Melanocortins have been involved in the regulation of the hypothalamic–pituitary–gonadal axis. While α-MSH released from melanotropes would mediate the suckling-induced PRL release, α-MSH administration in the ME of female rats inhibits the preovulatory prolactin and LH surge and ovulation (Crown et al., 2007). Caruso et al. (2004a) recently reported that central administration of α-MSH to adult male rats decreased serum LH levels through an interaction with MC4-R. Accordingly, it has been demonstrated that agouti-related protein (AgRP), an α-MSH antagonist, stimulates GnRH release and LH secretion, indicating the existence of an inhibitory melanocortinergic tone on LH that could be mediated by α-MSH (Vulléimoz et al., 2004).

Therefore, glutamate has a dual action on hypothalamic α-MSH release: NMDA receptor activation increases while group I and II mGluR activation decreases hypothalamic α-MSH release.

7. Involvement of mGluR activation in the regulation of GnRH release

The preovulatory surge of gonadotropin releasing hormone (GnRH) is essential for mammalian reproduction. Recent work has implicated glutamate and NO as having a key role in this process. Large concentrations of glutamate and its receptors are found in several hypothalamic nuclei known to be important for GnRH release (Brann, 1995). Administration of iGluR agonists stimulates GnRH and LH release, while iGluR antagonists attenuate the steroid-induced and preovulatory LH surge. Glutamate is believed to elicit many of these effects by activating the release of NO (Brann, 1995).

Very few studies have looked at the role of mGluR activation on LH and GnRH release.

Lopez et al. (1992) reported that a group I/II mGluR agonist did not affect GnRH release from ARC/ME fragments incubated *in vitro*. Accordingly, we observed that specific agonists for group I and II mGluRs produced no change in hypothalamic GnRH release and LH secretion *in vitro* in male rats (Pampillo et al., 2002b).

However, as we mentioned before, the activation of presynaptic group II/III mGluRs inhibits GABAergic input to GnRH neurons. Since GABA is implicated in the generation and modulation of the rhythm of GnRH release, mGluR could be affecting GnRH release (Chu and Moenter, 2005) Therefore, activation of mGluRs could inhibit GnRH release, at least in part, acting on GABAergic transmission. On the other hand, the increase of hypothalamic stimulatory factors such as oxytocin and substance P release induced by group I mGluR agonists may contribute to the stimulatory action of glutamate on LH release.

8. Effect of mGluRs on oxytocin and vasopressin release

Oxytocin is a nonapeptide that plays a significant role in the regulation of male and female sexual behavior, feeding behavior

and grooming, and it exerts important effects on the uterus and mammary gland. It is synthesized in magnocellular neurons of the SON and PVN and in accessory magnocellular nuclei of the hypothalamus (Silverman and Zimmerman, 1983). Following its synthesis, oxytocin is transported mainly along the neuronal axons to the posterior pituitary lobe, where it is stored until its secretion in neuronal terminals.

Glutamate can regulate hypothalamic oxytocin release through activation of AMPA and mGluRs (Pampillo et al., 2001). SON magnocellular neurons express group I mGluRs, though at less density than iGluRs (Meeker et al., 1994). Schrader and Tasker (1997b) found that the activation of group I mGluRs reduced K^+ currents in SON magnocellular neurons, whereas the activation of group II and III receptors had no direct effect on them, suggesting the presence of group I mGluRs in this hypothalamic area. In fact, we reported that group I mGluRs participate in the stimulatory effect of glutamate on hypothalamic oxytocin release in adult male rats (Pampillo et al., 2001). Morsette et al. (2001) also showed that group I mGluR activation increased oxytocin release in rat hypothalamo-neurohypophysial explants. In the posterior pituitary, our investigations show that NMDA significantly decreased oxytocin release while mGluRs agonists had no effect on the release of this hormone (Pampillo et al., 2001).

Oxytocin is also involved in the regulation of anterior pituitary hormone secretion. In particular, it affects the secretion of prolactin and LH. Oxytocin would have a differential effect on prolactin release being stimulatory at the level of the anterior pituitary and inhibitory in the hypothalamus. While hypothalamic oxytocin would not mediate the stimulatory effect of glutamate on prolactin release, this neuropeptide would definitely participate in glutamate's effect on LH release. Oxytocin stimulates the hypothalamic release of GnRH through an indirect mechanism that involves noradrenaline release and NO production (Van den Pol et al., 1990). Therefore, the increase in hypothalamic oxytocin release following AMPA/KA or group I mGluR activation would determine a rise in GnRH release, and consequently a stimulation of LH release from the anterior pituitary.

Vasopressin (VP), or antidiuretic hormone, contributes to hydric homeostasis and modulates blood pressure. Morsette et al. (2001) demonstrated a concentration-dependent stimulation of VP release when hypothalamo-neurohypophysial explants were perifused with group I mGluR agonists. The increase in VP release was probably due to the postsynaptic effects of group I mGluR agonists to depolarize magnocellular neurons. On the other hand, activation of group II mGluRs appears to have no effect on VP release (Schrader and Tasker, 1997b).

The increase in VP release in response to osmotic stimuli was not prevented by blocking postsynaptic group I mGluRs with a specific antagonist. Thus, despite the ability of group I mGluR agonists to induce VP release, these receptors are not required for osmotic stimulation. On the contrary, a group III mGluR agonist did induce a slight augmentation of basal and osmotically induced VP release (Morsette et al., 2001).

In Table 1, we summarized the actions of mGluR agonists on the release of some factors that have been implicated in the regulation of hormone secretion.

Table 1
Effects of mGluRs activation on several hypothalamic factors: (−) inhibited; (+) induced.

Effect of mGluRs activation on hypothalamic factors:							
	GABA	Dopamine	Substance P	α-MSH	CRH	Oxytocin	Vasopressin
mGluR	−	+[a]	+	−	+	+	+

Activation of groups I, II and III mGluRs inhibits GABA release, which in turn inhibits dopamine secretion, thus dopamine release could be indirectly induced. Activation of group I mGluRs induces substance P and oxytocin release, while groups I and II mGluRs inhibit alpha-MSH secretion. Moreover, groups I and III mGluRs activation increases vasopressin and CRH release.

[a] Probably, via GABA inhibition.

9. Effect of mGluR on adrenocorticotropic hormone (ACTH)

The hypothalamic – pituitary – adrenal (HPA) axis is the key regulator of the stress reaction. Dysregulation of this axis is thought to play a central role in the pathophysiology of anxiety and depressive disorders (Plotsky et al., 1998; Steckler et al., 1999; Holsboer, 2000; Posener et al., 2000; Lopez et al., 1998; De Kloet et al., 2005). Glutamatergic neurotransmission has long been implicated as a critical regulator of the stress response (Van den Pol et al., 1990; Brann, 1995). For example, glutamate stimulates ACTH secretion when injected i.c.v. (Darlington et al., 1989) or infused into the PVN of the hypothalamus (Makara and Stark, 1975). However, the relative contribution of individual glutamate receptor subtypes to the control of the HPA axis is unclear, yet.

mGluRs in particular appear to play a crucial role in mediating neuroendocrine responses to stress. ACPD, a non-selective mGluR agonist, induced a significant increase in plasma corticosterone following i.c.v. administration (Lang and Ajmal, 1995). This result would agree with studies from other groups, who reported an involvement of group I and group II mGluR in the regulation of the HPA axis. Johnson et al. (2001) reported that treatment with either agonist or antagonist of group I mGluRs results in a rise in serum corticosterone. The authors suggest that this paradoxical action may be due to a direct stimulatory effect of group I mGluR agonists on CRH release whereas selective mGluR1 and mGluR5 antagonists may increase CRH release through disinhibition of GABAergic interneurons. Accordingly, another study indicated that treatment with a selective mGluR5 antagonist increases circulating ACTH and corticosterone concentrations (Bradbury et al., 2003). On the other hand, an antagonist of group II mGluRs increased plasma corticosterone and CRH secretion from isolated hypothalami while group II mGluR agonists induced no modifications (Scaccianoce et al., 2003). The lack of effect of group II mGluR agonists supports the hypothesis that endogenous activation group II mGluR could tonically inhibit hypothalamic CRH release. If so, group II mGluR antagonists might become valuable tools for the study of efficiency of the HPA axis under physiological and pathological conditions, for example, during chronic stress or mood disorders.

Moreover, it has also been demonstrated that i.c.v. administration of the non-selective group III mGluR agonists L-AP4 and L-SOP induced an increase in corticosterone levels (Johnson et al., 2001).

Mitsukawa et al. (2006) showed altered corticosterone levels and feedback regulation in mGluR7−/− mice, suggesting that mGluR7 may play a role on the increase in stress hormones induced by group III mGluR agonists. The mechanism underlying this increase is currently unclear. However, group III mGluRs regulate the activity of GABA interneurones in the hypothalamus (Schrader and Tasker, 1997a) by decreasing L-glutamate release. Thus, there would be a decreased tone in GABAergic interneurons and a disinhibition on CRH neurons. Alternatively, it has been speculated that group III mGluR agonists might be acting directly on presynaptic terminals of the GABAergic interneurones (Johnson et al., 2001; Tasker et al., 1998). Both scenarios might explain how the absence of mGluR7 leads to a state of neuroendocrine dysfunction, which may subsequently induce an altered response in stress-related behaviors. Finally, AMN082, an allosteric agonist of mGluR7, induced a robust increase in stress hormone levels that was absent in mGluR7 knockout animals (Conn and Niswender, 2006) providing powerful support to a growing set of findings that suggest that

antagonists of this receptor may be useful in conditions involving chronic stress such as depression and anxiety disorders.

In summary, endogenous activation of group I and III mGluRs increases stress hormone release whereas group II mGluR would exerting a tonic control on mild stress.

10. Effect of mGluR on thyroid stimulating hormone (TSH)

Glutamate plays a role in the central regulation of the hypothalamic–pituitary–thyroid (HPT) axis. Wittman et al. (2005) found that glutamate transporter VGLUT2 axons established juxtapositions with all parvocellular TRH-synthesizing neurons of the PVN. These findings demonstrate that glutamatergic neurons directly innervate hypophysiotropic TRH neurons in the PVN and, therefore, support the hypothesis that the glutamate-induced activation of the HPT axis may be accomplished by a direct action of glutamate on hypophysiotropic TRH systems.

Villalobos et al. (1996) classified pituitary cells based on the responses to hypothalamic factors and found that the expression of functional TRH and glutamate receptors is closely associated and takes place in the same cells. TRH increases TSH release, which in turn stimulates the synthesis and release of hormones from the thyroid gland. To date there is no available data about the effect of mGluR on TRH and TSH release.

11. Effect of mGluRs on growth hormone (GH) release

GH release is mainly controlled by the interaction between two hypothalamic signals: GH-releasing hormone (GHRH) and somatostatin.

Aguilar et al. (2005) showed changes in GH secretion following administration of mGluRs agonists to prepubertal animals: a significant decrease in serum GH concentrations after central (i.c.v.) administration of *t*-ACPD (a group I and II mGluRs agonist) and following systemic administration of ibotenic acid (a weak agonist of all mGluRs). We have showed the presence of group II mGluRs in somatotropes and we observed an apoptotic effect of LCCG-I, a group II mGluRs agonist, on this cell type (Caruso et al., 2004b). The mGluR inhibitory effects contrast with the potent stimulatory actions observed following iGluR activation (Aguilar et al., 2005). Thus, it becomes apparent that L-glutamate is able to conduct a dual regulatory action upon GH secretion, which involves a predominant stimulatory effect via iGluRs, as well as a minor inhibitory effect via mGluRs.

12. Effect of mGluRs on prolactin (PRL) release

Control of PRL production and secretion from lactotropes of the anterior pituitary gland is thought to be determined primarily by the levels of dopamine released from the ARC. Dopamine exerts a physiologically relevant, inhibitory effect on PRL secretion through activation of D2 receptors. However, different studies suggest that there are prolactin-releasing factors (PRFs) that control hormone secretion independent of, or in concert with, endogenous dopamine levels. These PRFs would be peptides produced by neurons located within the hypophysiotropic area of the hypothalamus (Lamberts and Macleod, 1990; Reichlin, 1998; Ben-Jonathan et al., 1989).

Glutamate regulates basal PRL secretion and it 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, VIP, oxytocin and/or inhibiting factors such as dopamine and GABA (Brann and Mahesh, 1997; Lasaga et al., 1998). The information available suggests that glutamate increases prolactin secretion via NMDA receptors (Nagy et al., 2005).

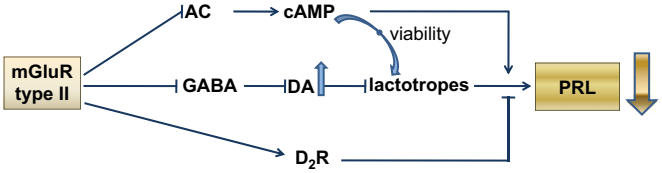

Fig. 1. Mechanisms involved in the modulation of prolactin (PRL) by group II mGluRs. Adenylate cyclase (AC) induces cAMP release which favors lactotropes survival and induces PRL secretion from pituitary cells. Activation of group II mGluRs inhibits AC, leading to a decrease in PRL release. Moreover, reduction of GABA release induced by group II mGluRs also leads to a PRL decrease via a disinhibition of dopamine release. Moreover, agonists of group II mGluRs may act as partial dopamine D_2R agonists, mimicking the inhibitory action of dopamine.

Group I mGluR activation reduces GABA release from the hypothalamus of male rats (Pampillo et al., 2002a) and this decrease could mediate the stimulatory action of glutamate on PRL release.

Although the principal site of action of glutamate is the hypothalamus, this neurotransmitter can also act on lactotropes (Pampillo et al., 2002b). In fact, glutamate may have a dual direct effect on PRL release from anterior pituitary cells of female rats: it exerts a stimulatory action when it interacts with iGluRs while it has an inhibitory effect when it activates group II mGluRs. Caruso et al. (2004b) demonstrated that group II mGluRs are present in lactotropes in the rat anterior pituitary, and their presence is consistent with functional data showing that LCCG-I, a group II mGluR agonist, decreases PRL release from the anterior pituitary gland (Caruso et al., 2004b). Since a cAMP analog reduced the inhibitory effect of glutamate on PRL release, group II mGluRs would participate in the inhibitory effect of glutamate on PRL release by reducing adenylate cyclase activity (Caruso et al., 2004b). On the other hand, group I and III mGluRs do not appear to be involved in the regulation of PRL secretion.

In summary, glutamate exerts a stimulatory action on prolactin secretion through iGluRs affecting the release of prolactin inhibitory and stimulatory factors from hypothalamic neurons. On the other hand, glutamate, via group II mGluRs, inhibits PRL secretion acting directly on the anterior pituitary.

Besides, we showed that LCCG-I affected the viability of anterior pituitary cells (Caruso et al., 2004b). Both glutamate and LCCG-I induced apoptosis in lactotropes indicating that the cytotoxic action of glutamate is mainly exerted on this cell type through activation of group II mGluRs, which are present in both cell types (Caruso et al., 2004b). A cAMP analog reduced the apoptotic effect of glutamate suggesting that group II mGluR activation triggers apoptotic events in the anterior pituitary via a decrease of cAMP synthesis (Caruso et al., 2004b).

As we mentioned before, group II mGluR stimulation may increase the activity of tubero-infundibular dopaminergic neurons by inhibiting the GABAergic input (Johnson and Chamberlain, 2002). Dopamine exerts a tonic inhibitory effect on PRL release and reduces the proliferation of lactotropes via D_2 receptors (Sarkar et al., 2005). Moreover, dopamine induces apoptosis of these cells in the presence of estradiol (Radl et al., 2008). We proposed that some group II mGluR agonists, such as LY 354,740 and LY 379,268, can act as D_2 agonists (Seeman et al., 2008). We showed that both agonists effectively stimulate D_2^{high} (high-affinity state of D_2 receptors) to inhibit PRL release. Moreover, LY 379,268 is able to reduce hyperprolactinemia under several conditions (Johnson and Chamberlain, 2002). Therefore, it is likely the actions of the agonists *in vivo* have both glutamate and dopamine components of action. This is summarized in Fig 1.

13. Conclusions

It is well recognized that glutamate is an essential component of the neuroendocrine transmission line that regulates anterior

pituitary hormone secretion. While the ability of pharmacological agents acting at iGluRs to modulate the levels of hypothalamic and pituitary factors has been extensively investigated, there have been few reports on the effects mediated by mGluRs. The available data indicate that the activation of mGluRs plays a role in the neural control of hypophyseal hormones such as ACTH, PRL, GH and oxytocin.

mGluR agonists have been suggested to act primarily at the hypothalamic level modulating the release of inhibitory and stimulatory hypothalamic factors. Group I mGluR agonists stimulate substance P, oxytocin and vasopressin release, while they decrease hypothalamic GABA and alpha-MSH. Group II mGluR agonists decrease hypothalamic alpha-MSH release. Group III mGluR agonists decrease hypothalamic GABA and increase CRH release. Evidence suggests a role for group I and III mGluR subtypes in stress-related behavioral disorders.

Activation of Group II mGluR can directly decrease prolactin and GH secretion from the anterior pituitary and agonists, such as LY 354,740 and LY 379,268, act as dopamine D_2 receptor agonists.

Converging lines of evidence suggest that activation of mGluRs plays a role in setting a fine tune in hypothalamic neurotransmission which regulates pituitary secretion.

The mGluRs, especially the group I and group II mGluRs, have recently become attractive therapeutic targets for drug development for the treatment of CNS diseases, including drug abuse, while group III mGluRs are the least studied due to the lack of selective pharmacological tools. However, selective allosteric potentiators of mGluRs have been recently developed and hold promise as therapeutic agents. For example, a compound called AMN082, which acts as an allosteric agonist of mGluR7, increases the release of plasma stress hormones. This compound provides support to a set of findings that suggest that antagonists of this receptor may be useful in conditions involving chronic stress, such as depression and anxiety disorders.

On the other hand, compounds that antagonize mGluR2, mGluR3 and/or mGluR5 (e.g. LY 341,495, MSG0039, MPEP) which are currently in preclinical development for the treatment of neurological and psychiatric disorders can facilitate the release of neurotransmitters such as dopamine and modulate the release of oxytocin and prolactin. Since selective modulation of the different mGluRs subtypes could induce different hormone responses, considerations must be taken on account before choosing one treatment over another. Finally, mGluRs selective agonists may have an impact in the treatment of conditions involving chronic stress since they regulate neuroendocrine stress circuits involving the HPA axis and stress-sensitive hormones such as oxytocin and prolactin. Thus further investigations are needed to fully understand the neuroendocrine actions of mGluRs.

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