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Metabotropic Glutamate Receptors in Peripheral Tissues: Implications for Toxicology

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1. Introduction

Glutamate, the main excitatory neurotransmitter in the central nervous system (CNS), signals through ionotropic receptors (iGluRs), including AMPA, kainate and NMDA receptors, which are glutamate-gated ion channels and regulate rapid responses upon activation, and metabotropic receptors (mGluRs), which evoke slower responses through activation of intracellular transduction cascades. mGluRs are single peptide seven-transmembrane spanning proteins linked to intracellular G-proteins although it has been reported that G-protein-independent signalling can occur (Heuss et al., 1999). Eight different mGluRs (mGluR1–8) have been cloned and classified into three groups (groups I, II and III) based on sequence homology and the intracellular signal transduction pathways they activate. Group I metabotropic glutamate receptors include mGluR1 and mGluR5 subtypes, which activate phospholipase C and induce inositol triphosphate production and intracellular calcium mobilization. Group II mGluRs include mGluR2 and mGluR3 subtypes, whereas Group III mGluRs include mGluR4, mGluR6, mGluR7 and mGluR8 subtypes. All these receptors are negatively coupled to adenylyl cyclase signalling, resulting in inhibition of cyclic AMP production. Since mGluRs are expressed by neurons and glia near the synaptic cleft, where they modulate not only the effect of glutamate on the postsynaptic neurons but also the release of glutamate and other neurotransmitters, it is thought that the mGluR system has evolved as a modulating mechanism for controlling excitability into the CNS (Schoepp, 2001). Furthermore, several mGluR subtypes were shown to exert glial and neuro-protective actions in distinct pathological conditions (Bruno et al., 1998; Kingston et al., 1999; D'Onofrio et al., 2001; Ciccarelli et al., 2007; Durand et al., 2010). However, mGluRs have currently received much attention motivated by a strong belief in their potential as drug targets for treatment of anxiety disorders and schizophrenia (Lavreysen & Dautzenberg, 2008; Chaki et al., 2010; Mezler et al., 2010; Schlumberger et al., 2009; Moreno et al., 2009; Patil et al., 2007).

The strongest suggestion that mGluRs are not exclusively synaptic receptors derives from numerous studies that demonstrate the presence of functional mGluRs in a number of peripheral non-neuronal cells, many of which do not even originate from the neural crest (Nicoletti et al., 2007), shifting the role of these receptors from mere synaptic regulators to modulators of basic cell functions (such as cell proliferation, differentiation and survival)

and key mediators of peripheral tissue function and neuroendocrine events. Besides organs that receive direct glutamatergic innervations, such as the heart and the adrenal glands, peripheral mGluRs can be activated in the absence of synaptic glutamate because of the existence of a large metabolic glutamate pool into cells derived from the Krebs cycle (Nicoletti et al., 2007). Then, metabolic glutamate can be transported outside the cell where it activates paracrine or autocrine mechanisms on cells expressing glutamate receptors.

As implied by the evidence above, the use of selective mGluR agonists and antagonists as therapeutic agents in treatment of anxiety disorders rises the problem of undesirable side effects in these patients. Therefore, in an effort to warn against unsafeness of clinical trials in the area of the anxiety disorders, this chapter summarizes current knowledge of the distribution and actions of mGluRs outside the brain.

2. mGluRs and anxiety

Several mGluR ligands were proved to have high efficacy for treatment of anxiety disorders: the mGluR1 antagonist JNJ16259685 and the mGluR5 antagonist MPEP showed anxiolytic effects in rodents (Spooren et al., 2000; Steckler et al., 2005a); group II mGluR agonists LY354740, LY379268 and LY404039 showed therapeutic actions in both anxiety and schizophrenia (Schoepp, 2004), whereas LY2140023 is entering phase II/III trials for schizophrenia (Eli Lilly, 2010).

While benzodiazepines exert their anxiolytic effect by binding to the γ -aminobutyric acid (GABA) receptors enhancing the inhibitory action of GABA in the CNS (Stahl, 2000); buspirone acts as a serotonin (5-HT)_{1A} receptor agonist (Ninan et al., 1998); propranolol is a β -blocker which arrests the autonomic arousal experienced during stress and anxiety (Noyes, 1985); and hydroxyzine is an antihistamine (Choy, 2007), the mechanism of anxiolytic action of mGluR ligands has not been completely elucidated. Currently, it is believed that their anxiolytic effects correlate with suppression of enhanced glutamatergic excitation at brain synapses involved in fear/anxiety in animals and humans (Schoepp et al., 2003), an action which is related to the synapse modulating function of these receptors. In addition, mGluR2/3 agonists regulate dopamine release and 5-HT_{2A} receptor activity, which have been presumed to be involved in their antipsychotic action (Chaki et al., 2010).

It is now known that typical antipsychotic administration derives in multiple side effects such as extrapyramidal symptoms, tardive dyskinesia, hypertension or weight gain. Benzodiazepines, for example, although effective and well tolerated, present associated risks including drug-drug interactions, pregnancy problems, psychomotor impairment, memory problems, and physiologic dependence (Choy, 2007). More recently developed atypical antipsychotics like risperidone or clozapine also were associated with weight gain, diabetes, hyperlipidemia, arrhythmia, hyperprolactinemia-related sexual dysfunctions, dystonic reactions, caratact, and insomnia (Üçok & Gaebel, 2008). Therefore, it is noteworthy that mGluR ligands with antipsychotic properties were not shown to induce the commonest adverse effects at date. However, mGluR agonists/antagonists may present a different set of adverse effects, considering their vast range of target peripheral organs.

3. mGluRs in endocrine organs

The initial demonstration of a role for glutamate on neuroendocrine regulation resulted from the observation that neonatal administration of monosodium glutamate was followed

by brain lesions and obesity (Olney, 1969). Later, glutamate was shown to act on endocrine function mostly by modulating hypothalamic activity which in turn alters hormone release, but can also activate its receptors on pinealocytes, pancreatic cells, adrenal and sexual glands, further regulating hormone production and endocrine homeostasis.

Both glutamate and its receptors are localized in a variety of hypothalamic nuclei considered critical for reproduction and neuroendocrine function. mGluRs have been found not only in different regions within the hypothalamus such as the paraventricular nucleus (PVN), the ventromedial (VMN), arcuate (ARC), supraoptic (SON) nuclei and the preoptic area (POA), but also in the three lobes of the pituitary gland (Meeker et al., 1994), exerting regulatory actions on the hypothalamic-pituitary axis.

3.1 Effects of mGluRs on prolactin release

Glutamate regulates basal prolactin secretion and also affects the physiological response of this hormone to stimuli such as suckling and stress (Nagy et al., 2005). Johnson & Chamberlain (2002) suggested that LY379268, a group II mGluR agonist, produces disinhibition of tubero-infundibular dopamine release, which in turn increases prolactin secretion.

On the other hand, we demonstrated that group II mGluRs are present in lactotropes in rat anterior pituitary, which tallies with functional data showing that L-CCG-I, a group II mGluR agonist, decreases prolactin release from anterior pituitary gland (Caruso et al., 2004). We also showed that L-CCG-I induces apoptosis in lactotropes (Caruso et al., 2004), which may account for the inhibition in prolactin secretion exerted by these receptors.

Interestingly, we also observed that group II mGluR agonists LY379268 and LY354740 may have a partial dopamine agonist action since they bind to D2 receptors in rat striatum and to human cloned D2Long receptors in CHO cells (Seeman et al., 2008). This action could lead to an inhibition of prolactin release from anterior pituitary cells. Concordantly, LY379268 can reduce hyperprolactinemia under several conditions in rats (Johnson & Chamberlain, 2002). It is likely that the actions of these agonists *in vivo* involve both glutamate and dopamine components (Cartmell et al., 2000).

All these facts agree with the lack of hyperprolactinemia, one of the most frequent side effects of antipsychotic drugs, after mGluR ligand administration (Patil et al., 2007).

3.2 Effects of mGluR activation on hypothalamic neuropeptide release which regulates LH secretion

Evidence from our laboratory indicates that glutamate-induced release of substance P (SP) in the rat ARC and median eminence is mediated via activation of NMDA and group I mGlu receptors (Caruso et al., 2006). Since SP has been shown to stimulate prolactin and luteinizing hormone (LH) secretion, induction of SP release may mediate, at least in part, the stimulatory effect of glutamate on LH and prolactin secretion (Debeljuk & Lasaga, 1999).

Glutamate can regulate hypothalamic oxytocin release through activation of AMPA and mGlu receptors (Pampillo et al., 2001). Schrader & Tasker (1997a) found that activation of group I mGluRs reduced K⁺ currents in SON magnocellular neurons, 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. The increase in hypothalamic oxytocin release following group I mGluR activation would determine a rise in gonadotropin-releasing hormone (GnRH) release (van den Pol et al., 1990), and consequently a stimulation of LH release from the anterior pituitary. Interaction between oxytocin receptor and mGluR1 was proposed. In hypothalamic rat astrocytes, antagonism of mGluR1a leads to a decrease in oxytocin-induced $[Ca^{2+}]_i$ response whereas the agonist DHPG potentiates the oxytocin response (Kuo et al., 2009).

Morsette et al. (2001) demonstrated a concentration-dependent stimulation of vasopressin (VP) release when hypothalamo-neurohypophyseal explants were perfused with group I mGluR agonists.

Activation of both group I and II mGluRs decreases alpha melanocyte stimulating hormone (α -MSH) release from hypothalamic fragments (Pampillo et al., 2002a). Since α -MSH inhibits preovulatory prolactin and LH surge and ovulation of female rats (Crown et al., 2007), mGluRs activity at α -MSH level could lead to increased LH production.

It is widely accepted that glutamate plays important roles in controlling GnRH neuron excitability, probably acting at the preoptic region of the hypothalamus (Gu et al., 1999). Only small sub-populations of GnRH neurons have functional mGluRs (Iremonger et al., 2010). A subpopulation of GnRH neurons in the medial septum was found to be excited by group I mGluR agonists (Dumalska et al., 2008). Nevertheless, we also know that activation of presynaptic group II/III mGluRs inhibits GABAergic input to GnRH neurons. Since GABA is involved in generation and modulation of the rhythm of GnRH release, mGluR could be affecting GnRH release (Chu & Moenter, 2005). Therefore, activation of mGluRs could inhibit GnRH release, at least in part thereby acting on GABAergic transmission. On the contrary, Lopez et al. (1992) and Pampillo et al. (2002b) reported that group I and II mGluR activation did not affect hypothalamic GnRH release *in vitro*.

In summary, actions of group I mGluRs on SP, oxytocin, VP and α -MSH at hypothalamic level seem to indicate that the use of group I mGluR antagonists as anxiolytic drugs could ultimately lead to decreased prolactin and LH surge.

3.3 Effect of mGluRs on Growth Hormone (GH) release

Aguilar et al. (2005) showed changes in GH secretion following administration of mGluR 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 mGluR agonist) and following systemic administration of ibotenic acid (a weak agonist of all mGluRs). We have shown the presence of group II mGluRs in somatotropes and we observed an apoptotic effect of LCCG-I, a group II mGluR agonist, on this cell type (Caruso et al., 2004). 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 exert a dual regulatory action upon GH secretion, which involves a predominant stimulatory effect via iGluRs, as well as a minor inhibitory effect via mGluRs.

3.4 Actions of mGluR activation on hypothalamic–pituitary–adrenal (HPA) axis

HPA axis is the key regulator of stress reaction. t-ACPD induced a significant increase in plasma corticosterone following i.c.v. administration (Lang & Ajmal, 1995). Jonhson et al. (2001) reported that treatment with either an 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. Concordantly, 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 of group II mGluR could tonically inhibit hypothalamic CRH release.

It has also been demonstrated that i.c.v. administration of nonselective group III mGluR agonists L-AP4 and L-SOP induced an increase in corticosterone levels (Johnson et al., 2001). Mitsukawa et al. (2006) showed that mGluR7 subtype plays a role in the increase of stress hormones induced by group III mGluR agonists. AMN082, an allosteric agonist of mGluR7, induced a robust increase in stress hormone levels that was absent in mGluR7 knockout animals (Conn & Niswender, 2006). Group III mGluRs regulate the activity of GABA interneurons in the hypothalamus (Schrader & Tasker, 1997b) by decreasing L-glutamate release. Consequently, there would be decreased tone in GABAergic interneurons and a disinhibition of CRH neurons.

In summary, although the HPA axis is activated by mGluR1/5 antagonists and group III mGluR agonists, this effect does not seem to interfere with the anxiolytic role of these ligands.

3.5 Pancreas

Although the presence and function of iGluRs in pancreatic tissue is quite well defined, there is still no consensus regarding expression of mGluRs in pancreatic islets. Brice et al. (2002) found mGluR3 and mGluR5 mRNA and protein in rat and human islets of Langerhans; mGluR8 expression was detected in rat islets; and mGluR4 was detected in rat islets but not in α or β cell lines (therefore, they could be expressed in δ cells). In consonance with these findings, mGluR3, mGluR5 and mGluR8 activation improved release of insulin from a β cell line in the presence of glucose, although mGluR8 activation inhibited insulin release at higher glucose concentrations (Brice et al., 2002).

On the opposite side, Uehara et al. (2004) reported evidence for functional occurrence of mGluR4, but not other mGluRs, in alpha and F pancreatic cells, its activation showing an inhibitory effect on glucagon secretion by reducing cAMP production. Thus, mGluR4-mediated signaling pathway might provide a molecular basis for chemotherapeutics for hyperglycemia, one of the symptoms of type 2 diabetes. However, Tong et al. (2002) demonstrated mGluR8 (not mGluR4)-dependent inhibition of glucagon release from rat pancreatic islets. Taking a third position, Cabrera et al. (2008) found no effect of mGluR agonists on glucagon secretion using human islets.

In an animal model of diabetes, upregulation of mGluR5 causes cell damage and neurodegeneration (Anu et al., 2010). However, other authors reported that endogenous activation of mGluR5 is required for optimal insulin response to glucose in mice and is also involved in the correct glucagon response to insulin challenge (Storto et al., 2006). Intracerebroventricular injection of ACPD (a group I and II mGluR agonist) increases plasma glucose, insulin and glucagon levels (Lang & Ajmal, 1995). Adult mice lacking mGluR5 weighed significantly less than littermate controls and, on a high fat diet, mGluR5 $-/-$ mice weighed less and had decreased plasma insulin and leptin concentrations (Bradbury et al., 2005).

3.6 Pineal gland

Pinealocytes express mGluR3 and mGluR5. Indeed, group II mGluR agonists inhibit norepinephrine-stimulated melatonin synthesis and N-acetyltransferase activity, possibly involving the mGluR3 subtype expressed in rat pineal gland (Yamada et al., 1998). Glutamatergic communication system of the pineal gland may not only enable paracrine crosstalk among pinealocytes but also probably relies on interactions between pinealocytes and interstitial cells analogous to neuronal-glial signaling (Pabst & Redecker, 1999). The evidence indicates that sleep disruption can be associated with mGluR function.

4. Other organs

4.1 Kidney

In the rat kidney the presence of mGluR2/3 has been described in the juxtaglomerular apparatus and proximal tubules, suggesting that these receptors may be involved in electrolytes and water homeostasis (Gill & Pulido, 2001). In addition, strong immunoreactivity for mGluR2/3 was observed in granular cells of the afferent arteriole (Gill & Pulido, 2001), indicating a possible role in the control of renin release, a hormone which belongs to the renin-angiotensin system involved in regulation of electrolyte, fluid balance and blood pressure (Jackson et al., 1985). In human kidney, focal expression of mGluR4 was detected in the collecting duct (Chang et al., 2005), whereas positivity of a normal mouse glomerulus for mGluR7 was found along the glomerular basement membrane (Rastaldi et al., 2006).

4.2 Liver and gastrointestinal tract

One of the first studies reporting the presence of mGluRs in peripheral organs showed the ability of group I mGluR agonists to stimulate phosphoinositide hydrolysis in primary cultures of rat hepatocytes (Sureda et al., 1997). In subsequent studies, expression of mGluR5, but not mGluR1, and mGluR3 in rat liver was demonstrated (Do et al., 2007; Storto et al., 2000a). Moreover, mGluR3 were shown to be up-regulated in response to persistent hypoxic status such as fibrotic/cirrhotic conditions in rat liver macrophages, exerting a role in functional metabolism and viability in this tissue (Do et al., 2007), although it has been shown that an agonist of mGluR2/3 had no effect on rat hepatocyte death induced by anoxia (Storto et al., 2000a). On the contrary, endogenous mGluR5 activation is associated with liver damage induced by lipopolysaccharide and d-galactosamine (Jesse et al., 2009) or by acetaminophen in mice (Storto et al., 2003). In turn, selective blockade of mGluR5 protects against hepatocyte death induced by hypoxia (Storto et al., 2004) and oxidative stress (Storto et al., 2003) in rodents.

mGluR5 antagonists have proved to be useful in the treatment of gastroesophageal gastric reflux in clinical trials (Bolea et al., 2004; Zerbib et al., 2010). mGluR8 agonists also have protective effects on esophageal sphincter relaxation (Frisby et al., 2005). mGluR1-8 mRNA expression has been detected in different cell components of rat stomach mucosa (Nakamura et al., 2010), whereas intense mGluR2/3 protein staining was found in both parietal and endocrine cells, suggesting a role in the regulation of gastric acid and gastrin secretion (Gill & Pulido, 2001). mGluR1 is also located in glandular stomach and glutamate induces changes in the expression of pepsinogen (San Gabriel et al., 2007). mGluR1/5 signaling may increase intracellular pH in the duodenum (Akiba et al., 2009). The presence of mGluR2/3 and mGluR1/5 has been demonstrated in neurons of jejunum and ileum, suggesting that they may

play a role in the regulation of intestinal motility (Larzabal et al., 1999; Liu & Kirchgessner, 2000; Nasser et al., 2007). On the other hand, mGluR4 and mGluR7 are expressed in colon mucosa (Chang et al., 2005; Julio-Peper et al., 2010). Activation of mGluR7 in the colon could be a component of secretory disorders such as stress-induced diarrhea (Julio-Peper et al., 2010). mGluR8 is also present in the enteric nervous system and their activation by selective agonists increases colon motility (Tong & Kirchgessner, 2003).

Thus, apparently, no major adverse effects are expected to be induced by group I mGluR antagonists or group II mGluR agonists in the normal or anoxic/cirrhotic liver or in the gastrointestinal tract.

4.3 Reproductive system

Most currently available studies involving mGluRs in both female and male reproductive systems include only descriptive, anatomical analyses, although the unique distribution of mGluRs in sex organs suggests their participation in reproductive events such as germinal cell development, testicular development, sex hormone production and cyclic cell turnover. In humans, immunoreactivity for mGluR1 was restricted to Leydig cells of intertubular spaces, where their activation could likely stimulate testosterone synthesis. mGluR5 was highly expressed in human seminiferous tubuli and in the mid-piece and tail of mature spermatozoa, even though neither mGluR5 agonist nor antagonist changed human sperm motility (Storto et al., 2001).

A strong immunolabeling for mGluR2/3 is present in the oocyte, the theca, and granulosa cells in the macaque ovary (Gill et al., 2008). Likewise, in rat ovary, the oocyte showed intense staining for mGluR2/3, whereas the corpus luteum was moderately immunoreactive (Gill & Pulido, 2001). mGluR4 has been found in the human cervix and is weakly expressed in the endometrial glands (Chang et al., 2005). mGluR2/3 show positive immunoreactivity for the most superficial layer of the stratified squamous epithelium of the exocervix in rat uterus (Gill & Pulido, 2001). mGluR2/3 expression is predominant in proliferating ovarian and uterine structures, which indicates that its production may be cyclically regulated (Julio-Peper et al., 2011).

All this evidence indicates that these receptors may be involved in ovulation, fertilization, implantation of the ovum and excitability of the uterus (Gill & Pulido, 2001). However, the only studies actually establishing a relationship between mGluRs and reproductive events are those which demonstrated a physiological interaction between estrogen receptors and mGluRs in both neurons and astrocytes (Dewing et al., 2007; Kuo et al., 2009). In the brain, estrogen receptor α interacts with mGluR1 to increase $[Ca^{2+}]_i$ flux and to initiate lordosis behavior and increases neuroprogesterone synthesis, which is a necessary step for estrogen positive feedback (Micevych et al., 2010). On the other hand, females treated neonatally with kainate, the type I/II metabotropic agonist ACPD, or both agonists combined showed adult male sexual behavior, indicating the participation of these glutamate receptor subtypes in masculinization (Wright & McCarthy, 2009).

Therefore, this evidence supports actual mGluR-mediated reproductive events and implications for fertility rise regarding administration of mGluR ligands for psychiatric disorders. Likewise, mGluRs are involved in embryonic development, as mGluR3 induce differentiation of neural stem cells (Ciceroni et al., 2010) whereas a switch from high mGluR5 expression to mGluR4 expression is found in embryoid bodies resembling embryogenesis (Cappuccio et al., 2006).

4.4 Immune system and thymus

mGluR activation has been proposed to play a similar role in the nervous and the immune systems by counteracting negative glutamate effects (Boldyrev et al., 2005). Since high levels of glutamate inhibit the proliferation of T-cells, glutamate has been related to immune deficiency (Ferrarese et al., 2001). Most attention has been focused on mGluR expression in thymocytes and T lymphocytes. Thymocytes express group I and II mGluRs (Storto et al., 2000b). Another study showed the presence of group III mGluRs in thymic cells (Rezzani et al., 2003). Group III mGluR activation may lead to oxidative stress and cell death of peripheral lymphocytes, a deleterious action potentiated by the presence of NMDA (Boldyrev et al., 2004, 2005). On the other hand, glutamate, acting via mGluR1 and mGluR5, has beneficial effects on human peripheral lymphocytes against activation-induced cell death (Miglio et al., 2005) or by inhibiting apoptosis induced by anti-CD3 treatment (Chiocchetti et al., 2006).

Pacheco et al. (2004) demonstrated that mGluR1 expression in human peripheral lymphocytes is detected after activation of the T-cell receptor CD3 complex, whereas mGluR5 is constitutively present (Pacheco et al., 2007), indicating that the expression of mGluRs in these immune cells depends on T-cell activation.

An antagonist of mGluR5 increased IL-6 secretion whereas an mGluR1 antagonist decreased the release of IL6, among other pro-inflammatory cytokines such as TNF-alpha and IFN-gamma (Pacheco et al., 2006), suggesting different signaling pathways of these mGluR subtypes in lymphocytes. Moreover, glutamate via group I mGluRs, regulates the initiation of T-cell-mediated immune responses (Pacheco et al., 2006).

mGluRs also seem to play a role in the development of autoimmune-related disorders (Julio-Pieper et al., 2011). For example, activation of mGluR4 in dendritic cells might exert a protective effect by preventing unbalance in T helper cells in a model of multiple sclerosis (Fallarino et al., 2010).

4.5 Heart

In animal and human hearts mGluR expression and effects on cardiac function have been reported. In rat heart, mGluR1, mGluR2/3 and mGluR5 are localized preferentially in the atrial nerve terminals, ganglion cells, and elements of the conducting system (Gill et al., 1999). In mouse heart, Moore-Morris et al. (2009) identified the mGluR1b transcript, which is functional in ventricular cardiomyocytes. In macaque heart, mGluR2/3 and 5 were found in myocardial nerve fibers, atrial intramural ganglia and myocytes, ventricular and submyocardial myocytes, Purkinje fibers, and bundle of Hiss (Mueller et al., 2003). In the human heart, mGluR1 and 5 but not mGluR2/3 were found in atrial intramural ganglia, atrial and ventricular cardiocytes, and bundle of Hiss (Gill et al., 2007).

Regarding the participation of the mGluR system in heart function, it has been shown that anteroventral third ventricular region infusion of mGluR agonist t-ACPD produced dose-dependent rises in plasma vasopressin, arterial pressure and heart rate after 5 or 15 min, although t-ACPD administration into the cerebral ventricle had no effect on these variables (Yamaguchi & Watanabe, 2004). Accordingly, group I, II and III mGluR agonists produced significant increases in arterial pressure and heart rate, although the respective antagonists failed to inhibit these cardiovascular responses (Tsuchihashi et al., 2000).

Nevertheless, opposite results were reported by others as follows. Microinjection of t-ACPD into the commissural subnucleus of the nucleus tractus solitarii elicited bradycardia (Braga et al., 2006). Activation of mGluR1, mGluR2/3, mGluR4 and mGluR8 into the nucleus tractus solitarius of anesthetized male Wistar rats elicited depressor and bradycardic

responses (Viard & Sapru, 2002). Furthermore, activation of spinal group I, II and III mGluRs increased the mean blood pressure in anesthetized rats while, after blockade of NMDA receptors, low doses of group II mGluR agonists induced hypotension and bradycardia (Celuch & García, 2002), suggesting that the main effects of mGluR agonist administration on cardiovascular function may depend on the dose used. Other authors have postulated that, in general, group I and II mGluRs produce responses consistent with excitation of neurons involved in reducing sympathetic outflow, heart rate, and arterial pressure (Foley et al., 1999; Jones et al., 1999).

These contradictory results make our interpretation of mGluR effects on cardiac function difficult. However, no adverse cardiovascular reactions were reported after mGluR ligand administration in patients with anxiety disorders.

4.6 Sense organs

mGluR1 and mGluR4, present in mammalian taste buds, sense umami taste elicited by monosodium glutamate (Chaudhari et al., 2009). The function of taste mGluR1 may be relevant in the back of the tongue. mGluR2 and mGluR3 mRNAs were also found in the circumvallate papillae, in cells co-expressing gustducin (Toyono et al., 2007).

mRNAs for seven of the eight mGluRs are expressed in the olfactory system, their expression being particularly high in the accessory olfactory bulb (Castro et al., 2007). In fact, under control conditions, recurrent inhibition of principal neurons (mitral cells) in accessory olfactory bulb slices was completely eliminated by mGluR1 antagonists (Castro et al., 2007). It has been suggested that mGluR2 might be involved in behavior associated with pheromone chemosignals (Nolte & Meredith, 2005).

All mGluRs except mGluR3 have been identified in the retina, with a differential distribution depending on the cell layers of retina (Connaughton, 2005), whereas mGluR6 activation have physiological significance (Gerber, 2003). In fact, defects in mGluR6 gene lead to congenital stationary blindness (Julio-Pieper et al., 2011). mGluR8 were clearly found in photoreceptor terminals in mammalian retina (Brandstätter et al., 1998; Koulen et al., 1999), their activation causing a decrease in $[Ca^{2+}]_i$ in isolated rat photoreceptors (Koulen et al., 1999) and preventing glutamate excitotoxicity. mGluR1 and 5 may modulate responses of ON bipolar cells to neurotransmitters (Koulen et al., 1997). mGluR1/5, mGluR2 and mGluR4/7/8 have also been reported to be present in amacrine cells (Hartveit et al., 1995; Brandstätter et al., 1998) and rat ganglion cells (Akazawa et al., 1994; Hartveit et al., 1995).

Glutamate is thought to be the afferent neurotransmitter in the auditory system. In situ hybridization showed that mGluR1 alpha mRNA was expressed by type I and type II spiral ganglion neurons in the cochlea, although at low levels (Safieddine & Eybalin, 1995), suggesting that mGluR1alpha play a minor role in auditory transmission. Group I mGluRs expressed by SCC hair cells may serve as a mechanism for selective amplification of mechanically evoked transmitter release, thereby enhancing signal discrimination (Hendricson & Guth, 2002). Group I mGluRs contribute to neurotransmission between inner hair cells and afferent neurons in mammalian cochlea (Kleinlogel et al., 1999). Activation of group II mGluRs is able to increase the release of dopamine in guinea pig cochlea, via a disinhibitory mechanism involving local GABAergic fibers, reducing glutamate excitotoxicity (Doleviczényi et al., 2005). On the other hand, mGluR7 is expressed in hair cells and in spiral ganglion cells of the inner ear, being associated with age-related hearing impairment (Friedman et al., 2009).

The widespread distribution and multiple actions of mGluR subtypes in sense organs suggest possible deleterious effects of mGluR ligands on sense function.

4.7 Bone

Glutamate was identified in nerve fibers running through bone marrow in close contact with bone cells, suggesting that it may also act as a neuromediator in this tissue and may contribute to the regulation of bone remodeling (Chenu, 2002). Gu & Publicover (2000) reported expression of mGluR1 in rat femoral osteoblasts by RT-PCR, whereas only mGluR4 and 8 mRNAs were detected in rat cultured calvarial osteoblasts (Hinoi et al., 2001). The mRNA and protein for mGluR6 were identified in rat femoral marrow stromal cells from the osteoblast lineage, where their activation suppressed generation of nitric oxide, which is pivotal to bone physiology (Foreman et al., 2005). Occurrence of mGluR3, 5 and 8 mRNA was identified in mouse osteoclast, although only mGluR8 were found in mature osteoclasts (Morimoto et al., 2006). A specific mGluR8 agonist decreased KCl-evoked secretion of glutamate and bone degradation products (Morimoto et al., 2006). Therefore, glutamate, via mGluR8, is thought to exert negative autocrine feedback, keeping osteoclasts in a suppressed state and preventing osteoporosis. In fact, vesicular glutamate transporter 1 (VGLUT1)-/- mice develop osteoporosis (Morimoto et al., 2006).

Cultured rat costal chondrocytes express mGluR1, 2, 4 and 8 and a group III mGluR agonist inhibits parathyroid hormone secretion through cAMP inhibition (Wang et al., 2005). Furthermore, chondral mineralization is greatly inhibited by group II and III mGluR activation in cultured embryonic mouse metatarsals by a mechanism involving apoptosis mediated by the depletion of intracellular glutathione (Wang et al., 2006).

Thus, there could be major implications for bone remodeling and chondral mineralization impairment by mGluR system-associated anxiolytic drugs.

5. mGluRs, tumor growth and cancer development

Stepulak et al. (2009) compiled data demonstrating that glutamate receptors are expressed in a variety of cancer cell lines (of neuronal and non-neuronal origin) and tumors, i.e., glioma, colorectal and gastric cancer, oral squamous cell carcinoma, prostate cancer, melanoma and osteosarcoma. It is also believed that the metabolic properties of tumors combined with altered metabolism in patients with cancer contribute to abnormally elevated glutamate plasma concentrations in these patients (Dröge et al., 1988). In turn, this excess of glutamate may activate its receptors and trigger intracellular signaling pathways, which may affect growth, survival and proliferation of cancer cells (Stepulak et al., 2009).

mGluR2 and mGluR7 were found to be expressed in all U87-MG and U343 (glioma), SK-N-A-S (neuroblastoma), TE671 (rhabdomyosarcoma/medulloblastoma), MOGGCCM (astrocytoma), SK-LU-1 (lung carcinoma), HT29 and LS180 (colon adenocarcinoma), Jurkat E6.1 (T cell leukemia cells), RPMI 8226 (multiple myeloma), T47D (breast carcinoma), and FTC (thyroid carcinoma) cancer cell lines (Stepulak et al., 2009). Expression of the other 6 subtypes of mGluR varied between these cell lines, although they were present in most of them. Also, mGluR3 mRNA is increased by 5-fold in aldosterone-producing adenomas compared to normal human adrenal glands (Ye et al., 2007).

Ectopic expression of mGluR1 in human normal melanocytes, which normally lack this receptor, resulted in melanocyte hyperproliferation and transformation into malignant

tumors that set off distant metastases (Nicoletti et al., 2007; Marin & Chen, 2004). In the clinical setting, mGluR5 expression correlated with a decreased survival rate in patients with oral squamous cell carcinoma (Park et al., 2007) and an mGluR5 agonist increased tumor cell migration, invasion, and adhesion in human tongue cancer cells, an effect that was reversed by an mGluR5 antagonist (Park et al., 2007). On the contrary, in medulloblastoma, expression of mGluR4 was shown to be inversely related to tumor severity, spreading and recurrence (Iacovelli et al., 2006). Nevertheless, over-expression of mGluR4 was associated with poor prognosis in colorectal carcinoma (Chang et al., 2005) and their expression was identified in 68% of colorectal carcinomas, 50% of laryngeal carcinomas, and 46% of breast carcinomas (Julio-Pieper et al., 2011).

Concordant with the expression profile, pharmacological blockade of mGluR3 reduces cell proliferation and mitogen-activated protein kinase activation in cultured human glioma explants or glioma cell lines (D'Onofrio et al., 2003). Furthermore, systemic administration of the mGluR2/3 antagonist LY341495 inhibits the growth of glioma cells implanted either under the skin or inside the brain parenchyma of nude mice (Arcella et al., 2005). It is likely because of their neuroprotective role and the battery of trophic factors they induce that mGluR activation also stimulates glioma proliferation.

6. Concluding remarks

mGluRs play important neuromodulatory roles throughout the brain as such they are targets for therapeutic intervention for a number of psychiatric and neurological disorders including anxiety, depression, Parkinson's disease and schizophrenia.

Currently approved antipsychotic drugs have substantial extrapyramidal and metabolic side effects, but (beyond its high efficacy and ease of delivery) the advantage of use of mGluR ligands for the treatment of anxiety disorders is the lack of the commonest undesirable effects, which include alterations in prolactin levels, extrapyramidal symptoms, weight gain, glucose abnormalities, hypertension, sedation or Parkinsonian symptoms. The probability of a complete absence of adverse effects, however, does not seem to be very high because, as implied by the evidence compiled in this chapter, the implications of mGluR ligands toxicity are many and far-reaching.

mGluR1 selective antagonists showed efficacy in rodent models of anxiety, however, these compounds were associated with memory impairment that interrupted further development (Steckler et al., 2005a,b; Gravius et al., 2005). On the other hand, mGluR5 selective antagonists, which also has anxiolytic efficacy did not cause impairment in memory (Steckler et al., 2005a; Gravius et al., 2005).

As reported (Mezler et al 2010; Chaki et al 2010; Patil et al 2007), the latest developed allosteric group II mGluR agonists have efficacy in preclinical models of psychosis and anxiety, without involving any of the most frequent side effects associated with typical and atypical antipsychotics. Nevertheless, the ubiquity of mGluRs in peripheral tissues and the broad spectrum of possible side effects signify that the reported measurements are far from exhaustive. Consequently, some "silent" or long term unacceptable side effects on other target organs might be associated with mGluR agonist administration and should be considered. Endocrine alterations such as changes in LH, GH or oxytocin levels induced by group I mGluR ligands should be taken into consideration. Furthermore, fertility impairment and embryogenesis defects, immune deficits, sense function impairment and osteoporosis induced by group II mGluR activation are issues to be further studied. Finally,

tumor development after mGluR ligand administration represents another possible risk to be further investigated. Hence, there is a need for screening and monitoring for all these possible problems, which are not considered in current clinical trials.

7. References

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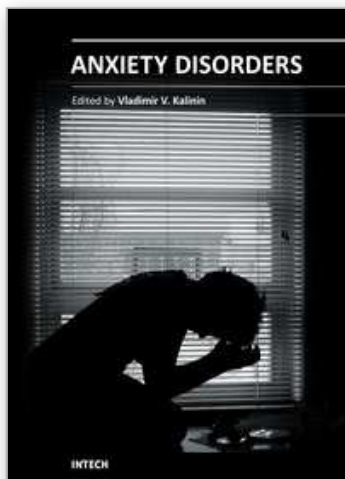
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