

Pharmacological regulation of striatal gene expression by metabotropic glutamate receptors

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ABSTRACT

Metabotropic glutamate receptors (mGluR) are densely expressed by striatal medium spiny neurons. Activation of mGluR in this brain region alters local transmitter release and behaviors of experimental animals. In particular, mGluR regulate transcription factor and neuropeptide gene expression in striatal neurons through their connections with multiple intracellular effectors. This prominent involvement of mGluR in overall cellular activity is pivotal for the development of neuronal plasticity underlying long-term adaptive changes in cellular physiology related to a variety of neurologic disorders. Accumulating evidence demonstrates that the subtypes of mGluR have distinct effects on gene expression; group I subtypes facilitating, and group II/III subtypes inhibiting, gene expression. Thus, the mGluR can be considered as promising targets in the development of novel therapeutic drugs that can relieve neurologic disorders resulting from dysfunction of the striatum.

INTRODUCTION

Metabotropic glutamate receptors (mGluR) are relatively novel members of the glutamate receptor family which are, through G-proteins, coupled to

multiple intracellular second messenger systems^[1]. So far, eight subtypes of mGluR (mGluR1-8) have been cloned. Like ionotropic receptors, they are heterogeneous in their distribution, pharmacology and connections with intracellular effectors. According to the intracellular responses to activation of the mGluR expressed in the *Xenopus* oocyte system, the eight subtypes are divided into three functional groups. Activation of group I (mGluR1 and mGluR5) mGluR increases phosphoinositide (PI) hydrolysis, whereas activation of group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) mGluR inhibits cAMP formation in an adenylate cyclase-dependent fashion^[1]. Linkages to diverse intracellular effectors allow mGluR to preferentially participate in the various slower effects, including nuclear DNA transcriptional activity (see below), brought about by modifying intracellular metabotropic activity, as opposed to rapid synaptic transmission mediated by ionotropic glutamate receptors.

Abundant glutamatergic projections from widespread areas of forebrain (cerebral cortex, thalamus, amygdala, hippocampus and prefrontal cortex) to the striatum, a central structure in the basal ganglia controlling movement, have been well documented in numerous morphological studies^[2]. A large proportion of extrinsic glutamatergic terminals make asymmetrical (excitatory) synaptic contact with the medium-sized spiny projection neurons (striatonigral and striatopallidal neurons)^[3,4]. Parallel with the rich glutamatergic afferents, mGluR which endogenous glutamate interacts with are densely distributed in the striatum. Quantitative receptor autoradiography reveals high levels of mGluR binding sites in the striatal region^[5]. Since a lesion of corticostriatal projections had no significance effect on mGluR binding quantity in the striatum, 90 %

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of mGluR are thought to be located on postsynaptic striatal neurons^[6]. Studies with *in situ* hybridization^[7-10] and immunocytochemistry^[11,12] show the presence of mGluR 1-5 and mGluR 7 in the rat striatum, with high levels of mGluR3 and mGluR5 and moderate levels of mGluR1 and mGluR4^[9,13]. Interestingly, mGluR2 was only expressed in a small population of large polygonal neurons, likely cholinergic interneurons^[9]. Given the anatomically enriched mGluR system in the striatum described above, it can be speculated that mGluR-mediated glutamatergic transmission might be intimately involved in the modulation of normal and stimulated striatal neuronal activity.

BEHAVIOR

Demonstrating the physiological roles of mGluR in regulating striatal functions started with behavioral investigations. Sucaan *et al*^[14] first reported that acute injection of the mGluR agonist, ACPD, into the unilateral striatum of adult rats caused rotation contralateral to the injection side. Similar findings were generally repeated afterwards in other laboratories^[15,16]. Since these behavioral changes were blocked by the mGluR antagonist MCPG, but not by ionotropic glutamate receptor antagonists, activation of mGluR is conceived to mediate the ACPD-stimulated behaviors.

Using subtype-specific agonists/antagonists, recent studies show that behavioral stimulation by mGluR is mediated via activation of group I, but not group II/III mGluR. Intrastratial infusion of the group I agonist DHPG at moderate to high doses induces hyperlocomotion and characteristic stereotypical behaviors, which are sensitive to the group I antagonist PHCCC, but not to the group II/III antagonist MSOPPE^[17]. Inhibition of intracellular Ca²⁺ release with intrastratial injection of dantrolene, an inhibitor of Ca²⁺ mobilization, is also effective in blocking behaviors induced by DHPG^[17] or ACPD^[18]. In contrast to the stimulating behavioral effects of group I mGluR activation, intrastratial infusion of the group II agonist DCG-IV or the group III agonist L-AP4 had no effect on spontaneous behavioral activity^[19]. Dopaminergic transmission seems necessary for the ACPD-stimulated behaviors^[16]. However, the DHPG-

stimulated behaviors were found to be independent of dopamine D₁ receptor stimulation^[17].

GENE EXPRESSION

A particularly interesting role that mGluR play in overall neuronal function is the modulation of intracellular activity, such as the DNA transcription (gene expression). Through connections to multiple second messenger systems, the activity of mGluR might be vigorously and preferentially linked to regulation of the transcription rate of certain DNA, a biochemical process called stimulus-transcription coupling. The genomic responses to mGluR stimulation can serve as an important component of the molecular/cellular mechanisms underlying neuronal plasticity. Thus, investigation of the role of mGluR in the regulation of gene expression might provide valuable insight into molecular formation of striatal neuronal plasticity related to a variety of neurologic disorders.

Immediate early genes (IEG) are among prime markers used in exploring receptor-mediated nuclear gene expression, because they are readily inducible in response to various physiological and pharmacological stimuli. The first experiment investigating the effects of mGluR on striatal gene expression was conducted in primary cultures from rat striatum^[20]. In this study, enhancement of mGluR activity by perfusion of the mGluR agonist ACPD elevated basal level of IEG *c-fos* mRNA in cultured neurons, indicating a positive linkage between mGluR activity and constitutive *c-fos* mRNA expression. Recent studies performed *in vivo* established an excellent similarity. Striatal mGluR stimulation by local ACPD injection elevated *c-fos* as well as another IEG *zif/268* mRNA expression in the rat striatum, an effect that was sensitive to an antagonist selective for mGluR (MCPG), but not for ionotropic NMDA (CPP) or dopamine D₁ receptors (Sch-23390)^[21]. This confirms the existence of positive stimulus-transcription coupling from mGluR to nuclear IEG expression in striatal neurons *in vivo*.

One of the most noticeable functions that IEG might play in mature neurons is to serve as third messengers in the stimulus-transcription coupling to induce so called late-response gene expression. In other words, IEG once rapidly induced via their own stimulus-transcription coupling mechanism can further

function as powerful transcription factors to regulate the expression of many other target genes. Such changes may last longer and may, therefore, be more directly related to long-lasting adaptive alterations in cellular physiology.

Indeed, acute injection of ACPD into the rat striatum dose-dependently elevated levels of mRNA of the neuropeptides prodynorphin and substance P contained by striatonigral neurons and preproenkephalin contained by striatopallidal neurons^[22]. The increases in opioid peptide (prodynorphin/preproenkephalin), although not substance P, mRNA expression were blocked by MCPG. Thus, striatal opioid peptide expression, like IEG induction, is also positively linked to mGluR activation. However, compared with the rapid and transient induction of *c-fos* and *zif/268* expression which usually peaked 1 h and disappeared by 3 h after mGluR stimulation^[21], the neuropeptide induction showed a delayed and prolonged pattern. It was evident at 2 or 3 h and lasted more than 10 h after ACPD injection^[22]. The time course for dynamic induction of the IEG and opioids appeared to indicate a possibility that the early induced IEG transcription factors might contribute to trigger, although might not contribute to remain, the following opioid induction. In support of this notion, intrastriatal injection of *c-fos* antisense oligonucleotides, which specifically interfere with functional Fos protein synthesis at the translational level, reduces dynorphin-like immunostaining induced by a dopamine stimulant^[22].

D₁ dopamine receptor stimulation is well known to stimulate striatal IEG and neuropeptide gene expression^[23,24]. These genomic responses are thought to contribute to the development of neuronal plasticity important for long-term changes in behaviors (sensitization, tolerance, addiction and withdrawal syndrome) induced by indirect dopamine receptor agonists, such as cocaine or amphetamine^[25-27]. Since striatal glutamatergic transmission is, like dopaminergic transmission, implicated in the biological actions of these psychotropic drugs (for reviews, see Ref 2, 28), it is intriguing to examine the profile of mGluR-sensitive glutamate pathways in stimulant-induced gene expression. It was found that, in the presence of the mGluR antagonist MCPG, amphetamine no longer produced significant induction of either IEG (*c-fos* and *zif/268*) or neuropeptides (prepro-

dynorphin, substance P and preproenkephalin) gene expression in the striatum^[29]. Moreover, unlike a D₁ dopamine receptor antagonist which blocks both behavior and gene expression^[23,24], the mGluR antagonist selectively blocked the gene expression, but sparing the behaviors, in response to acute amphetamine in naive animals. This is in strong favor of the speculation that mGluR function as a modulator specifically involved in the effects of the drug on target DNA transcription in striatal neurons rather than typical synaptic transmission. Through this modulatory effect, mGluR contribute to reset neuronal responsiveness to subsequent stimulation which is manifested by altered behavioral responsiveness to subsequent drug exposure.

SUBTYPE-DEPENDENT REGULATION OF GENE EXPRESSION

Although the mGluR agonist ACPD is not subtype specific, the gene expression stimulated by this agent is most likely mediated by group I mGluR. Activation of group I mGluR increases PI hydrolysis which gives rise to two products, diacylglycerol (DAG) and inositol 1, 4, 5-triphosphate (IP₃). The former activates protein kinase C (PKC) whereas the latter releases Ca²⁺ into the cytoplasm from intracellular Ca²⁺ stores by interacting with IP₃ receptors densely expressed in striatal neurons^[11]. ACPD has been confirmed to liberate Ca²⁺ from non-mitochondrial internal stores in cultured striatal neurons^[30]. Recent evidence from *in vitro* neuronal cells indicates that Ca²⁺ and its major protein kinase substrate, Ca²⁺/calmodulin-dependent protein kinase II (CaMK II) which is highly expressed in striatal neurons^[31], can serve as an effective signaling pathway to transmit extracellular stimuli to the cytoplasm, and then to the nucleus to stimulate gene expression^[32,33]. This scenario, as illustrated in (Fig 1), starts with enhancement of cytosolic free Ca²⁺ through increased Ca²⁺ influx by pharmacologically manipulating voltage-operated Ca²⁺ channels or ligand-gated Ca²⁺ channels, such as NMDA receptors. The elevated Ca²⁺ activates CaMK II^[34], which in turn phosphorylates the transcription factor, cAMP response element binding protein (CREB). The phosphorylated CREB will eventually increase *c-fos* transcription by interacting the specific site in the promoter region of

c-fos DNA in a sequence-specific manner. Hence, Ca^{2+} -CaMK II-CREB forms a complete cascade to transmit the Ca^{2+} signal into the gene expression. However, this cascade was identified in response to the Ca^{2+} signal induced by Ca^{2+} influx. It remains to be proven experimentally whether the same cascade works in response to Ca^{2+} released from intracellular stores following mGluR activation. This is especially important since it was recently recognized that Ca^{2+} signals increased by different mechanisms may have different effects on cellular function, including gene expression^[35]. In addition, all studies described above were performed *in vitro*. It is now necessary to dissect and characterize the roles of the Ca^{2+} /CaMK II/CREB pathway in gene regulation in more complicated *in vivo* conditions.

Group I mGluR may also stimulate gene expression through the DAG-dependent PKC pathway (Fig 1). PKC is among the protein kinases which are highly concentrated in medium spiny neurons, but not in glia^[36]. mGluR stimulation in cultured striatal neurons causes a translocation of PKC from a cytoplasmic (soluble) form, prevalent in resting conditions, to a membrane-bound form, a mode of activated PKC^[37], and concomitant IEG induction which is sensitive to a PKC inhibitor^[30].

In contrast to positive modulation of gene expression by group I receptors, group II/III receptors affect gene expression in an inhibitory fashion (Fig 1). Through the inhibition of adenylate cyclase activity, the group II/III receptors could confine excitatory responses of the cAMP/PKA/CREB pathway well known to induce gene expression in striatal neurons^[38,39] after stimulation of G_i -protein coupled receptors, such as the D_1 dopamine receptor. Indeed, when selective stimulation of group II mGluR was made by using a subtype-specific agonist DCG-IV, dopamine-stimulated neuropeptide mRNA expression became much less in striatal neurons (Wang *et al*, unpublished observation).

mGluR might also regulate gene expression indirectly by affecting presynaptic transmitter release (Fig 1). Although mGluR appear to be anatomically organized to exert the major postsynaptic regulation of striatal neuronal activity given that 90% of mGluR in the striatum are located on neurons^[6], presynaptic modulation of transmitter release by a small proportion

of mGluR can be significant if they are highly sensitive. Early *in vitro* studies demonstrated a negative feedback mechanism controlling glutamate outflow, probably via presynaptically located mGluR (inhibitory autoreceptors). mGluR stimulation by ACPD inhibited endogenous glutamate release from rat striatal synaptosomes^[40,41]. However, recent *in vivo* studies using the microdialysis technique produced opposite results. Infusion of the mGluR agonist ACPD at high concentrations facilitated striatal glutamate release in conscious or anesthetized rats^[42,43]. The difference between *in vitro* and *in vivo* studies may reflect an existence of dual modulatory effects of mGluR on glutamate release, depending upon the subtypes stimulated. Through inhibition of cAMP formation, group II/III receptors, which are expressed by corticostriatal and thalamostriatal neurons and possibly distributed on their terminals^[6,44], suppress tonic and phasic glutamate release^[45,46]. In contrast, group I receptors facilitate glutamate release via activation of the PL/Ca^{2+} pathway. Operation of this positive feedback can cause excessive glutamate release, which might eventually result in excitotoxicity^[47] or pathophysiological gene expression.

ACPD also increases extracellular dopamine levels in the rat striatum^[48-51]. Mechanisms underlying this increase may involve presynaptic mGluR (heteroreceptors) if their presence on dopaminergic terminals can be definitively proven. Alternatively, the altered dopamine release may be an event secondary to the altered release of glutamate or any other local transmitters, and vice versa. Similar to glutamate, a subtype-driven dual regulation mechanism may also apply to mGluR-sensitive dopamine release. The group I mGluR agonist DHPG reportedly has either no or facilitates dopamine release, whereas group II and III agonists (DCG-IV and L-AP4, respectively) inhibit striatal dopamine release^[52].

Because mGluR antagonists had no or little effect on basal levels of IEG and peptide gene expression^[21,22,39], the mGluR-sensitive regulation of IEG and peptide expression may not be active in normal physiological conditions. This is in sharp contrast to the driving forces from ionotropic glutamate receptors and other receptors needed for constitutive expression of these mRNAs in this brain area^[53-55]. It is reported that ionotropic receptors occupy the 'core' of the

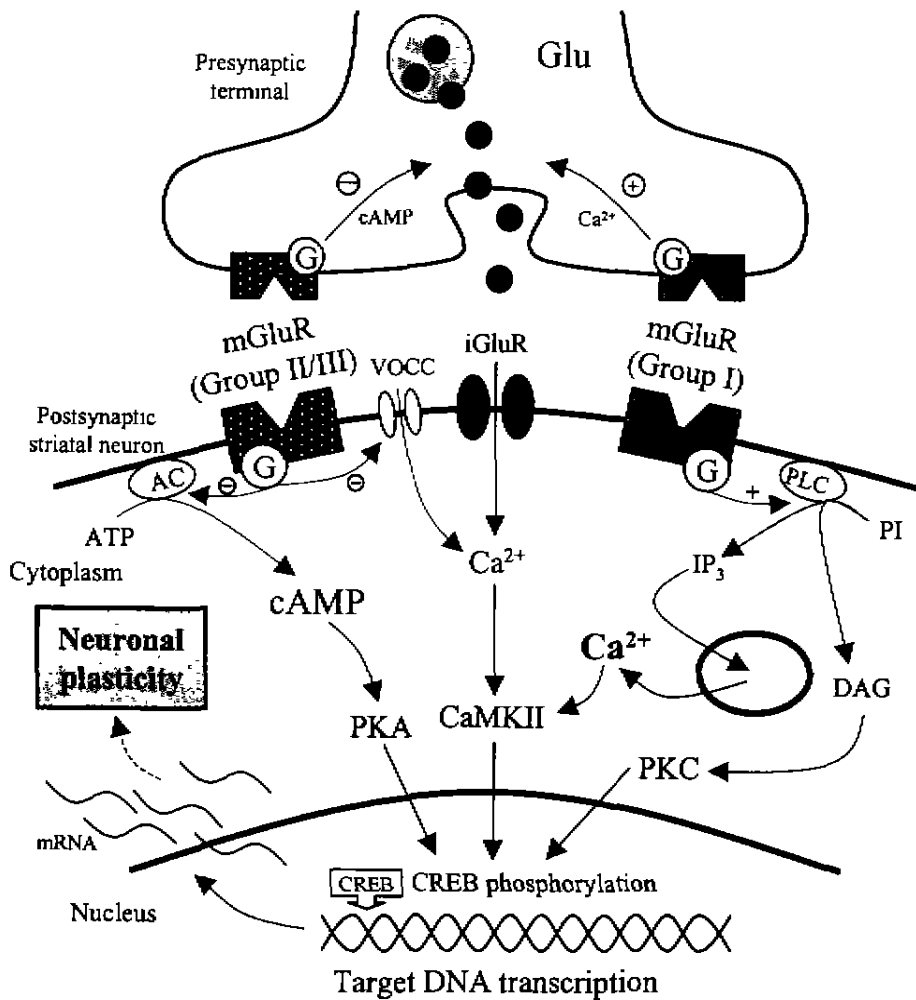


Fig 1. Schematic illustration of the roles of metabotropic glutamate receptor (mGluR) subtypes in the regulation of gene expression related to neuronal plasticity. At the postsynaptic level, group I receptors enhance intracellular Ca^{2+} concentration by releasing Ca^{2+} from intracellular stores, as opposed to Ca^{2+} influx through voltage-operated Ca^{2+} channels (VOCC) or ionotropic glutamate receptors (iGluR) that are Ca^{2+} permeable, in particular NMDA receptors. Signal Ca^{2+} is powerful stimulator of gene expression likely through activation of Ca^{2+} /calmodulin-dependent protein kinase II (CaMK II). Alternatively, group I receptors would positively regulate gene expression via the diacylglycerol (DAG)/protein kinase C (PKC) pathway. Group II/III receptors, in contrast, suppress gene expression by inhibiting the cAMP/protein kinase A (PKA) pathway, the well-known pathway inducing gene expression in response to D_1 dopamine receptor stimulation. At the presynaptic level, group I receptors augment glutamate (Glu) release whereas group II/III receptors inhibit glutamate release. Through this presynaptic modulation mGluR can indirectly regulate gene expression in postsynaptic striatal neurons. Other abbreviations: AC, adenylate cyclase; CREB, cAMP response element binding protein; G, G protein; IP_3 , inositol 1,4,5-triphosphate; PI, phosphoinositide; PLC, phospholipase C.

synapse as opposed to mGluR which localize at the periphery of the postsynaptic membrane^[56,57]. As a result, full activation of mGluR may occur only when massive endogenous glutamate is released or a high dose

of an exogenous agonist is given. This use-dependent engagement of the mGluR may give this type of glutamate receptor a great advantage over other receptors as a better target for therapeutic drug

development.

In summary, as an important element of glutamatergic transmission enriched in the striatum, mGluR activity is linked to most aspects of striatal function. Initial studies reveal that mGluR-mediated glutamatergic signaling controls movement and local transmitter release. Recent experiments demonstrate mGluR-sensitive stimulus-transcription coupling in the regulation of IEG and neuropeptide gene expression in normal and stimulated conditions. This makes particular sense for this type of glutamate receptor in light of their unique relationship with multiple intracellular signaling systems. This also provides solid evidence for previously-proposed speculation that mGluR are preferentially involved in intracellular metabotropic activity, such as gene expression, in response to extracellular stimulation, which contributes to the formation of neuronal plasticity important for long-term adaptive changes in cellular physiology related to a variety of neurologic disorders. Since nuclear gene expression lies at the heart of signal transduction, development of small molecules that affect gene expression by influencing the activity of mGluR and/or their associated signal pathways represents a novel gene therapy approach to a variety of striatum-based neurologic disorders^[58,59].

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代谢型谷氨酸受体对纹状体神经元基因表达的调制作用

R 971.2

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关键词 兴奋性氨基酸类; 多巴胺;
即时早期基因; 成瘾行为; 基底神经节; 纹状体;
神经肽; 麻醉品
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