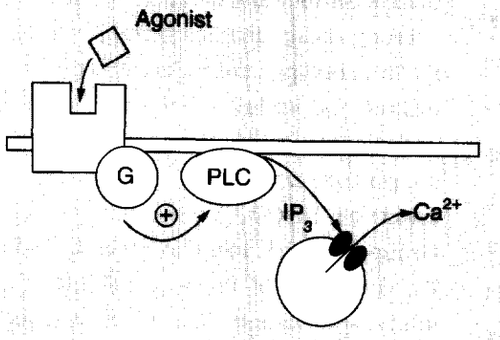
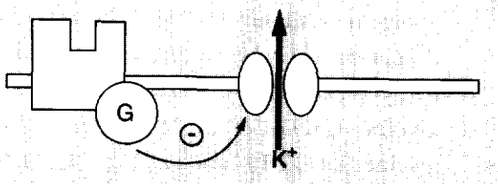
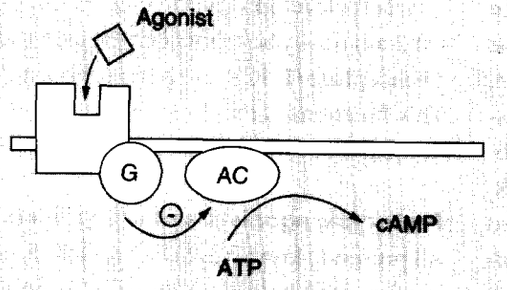
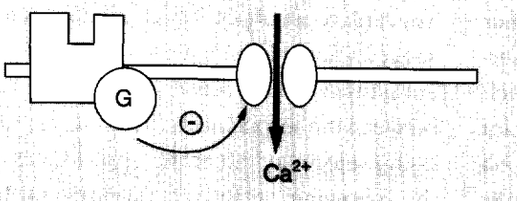
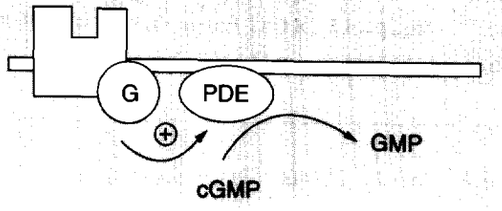
Box 1. Classification of mGluRs based on signal transduction mechanism and agonist selectivity[13]

The left two columns indicate the designation of the mGluR subtypes and their splice variants (see Refs 25,26) for groups I–III. Binding of an agonist at group I mGluRs results in a G protein-mediated activation of phospholipase C (PLC) and production of inositol triphosphate (IP_3) which releases Ca^{2+} from internal stores and causes an elevation in cytosolic free calcium concentration ($[Ca^{2+}]_i$). In nerve cells, activation of group I mGluRs results in a depression of various potassium currents (I_{K+}). Binding of an agonist at group II and group III mGluRs induces a G protein-mediated inhibition of adenylate cyclase (AC). Group III may also stimulate phosphodiesterases (PDE)[74]. Depressed AC activity reduces production of cyclic adenosine monophosphate (cAMP), and stimulation of phosphodiesterase decreases cyclic guanosine monophosphate (cGMP) concentration. In nerve cells, group II and group III mGluRs depress the activity of various calcium channels ($I_{Ca^{2+}}$). The right panels show the rank order of agonist potency for each group. (1*S*,3*R*)-ACPD, (1*S*,3*R*)-ACPD-1-aminocyclopentane-1,3-dicarboxylic acid. For other abbreviations see text and Figure 1.

Group	Signal transduction	Effect of activation	Rank order of agonist potency
I $mGluR_{1a}$ $mGluR_{1b}$ $mGluR_{1c}$ $mGluR_{5a}$ $mGluR_{5b}$		$[Ca^{2+}]_i$ ↑	Quisqualate > 3,5-DHPG > L-CCG-I > (1*S*,3*R*)-ACPD > L-AP4
		I_{K^+} ↓	
II $mGluR_2$ $mGluR_3$		cAMP ↓	DCG-IV > *trans* MCG-I > L-CCG-I > (1*S*,3*R*)-ACPD > quisqualate >> 3,5-DHPG, L-AP4
III $mGluR_{4a}$ $mGluR_{4b}$ $mGluR_6$ $mGluR_{7a}$ $mGluR_{7b}$ $mGluR_8$		$I_{Ca^{2+}}$ ↓	L-AP4 ≈ L-SOP >> (1*S*,3*R*)-ACPD > quisqualate, 3,5-DHPG
		cGMP ↓	

are shown in Figure 1, which illustrates their correspondence to a frozen extended[21] conformational state of glutamate.

Certain structural derivatives of these prototypic agonists have been found to act as antagonists at the respective subtypes (Figure 1). Thus, replacement of the weak acidic phenol substituents by a carboxylic acid on the aromatic ring of the phenylglycine turns the agonist (*S*)-3,5-DHPG into an antagonist (*S*)-4-CPG (carboxyphenylglycine). For groups II and III, the substituent at the α-position plays a critical role, and introduction of a methyl group into that position produces an antagonist as exemplified by α-methylcarboxycyclopropylglycine (MCCG-I) and α-methyl-2-amino-4-phosphonobutyric acid (MAP4)[22].

This scheme of prototypic agonists and antagonists has clear limitations, and further research is required to understand the SAR of mGluR subtypes. For instance, most phenylglycine

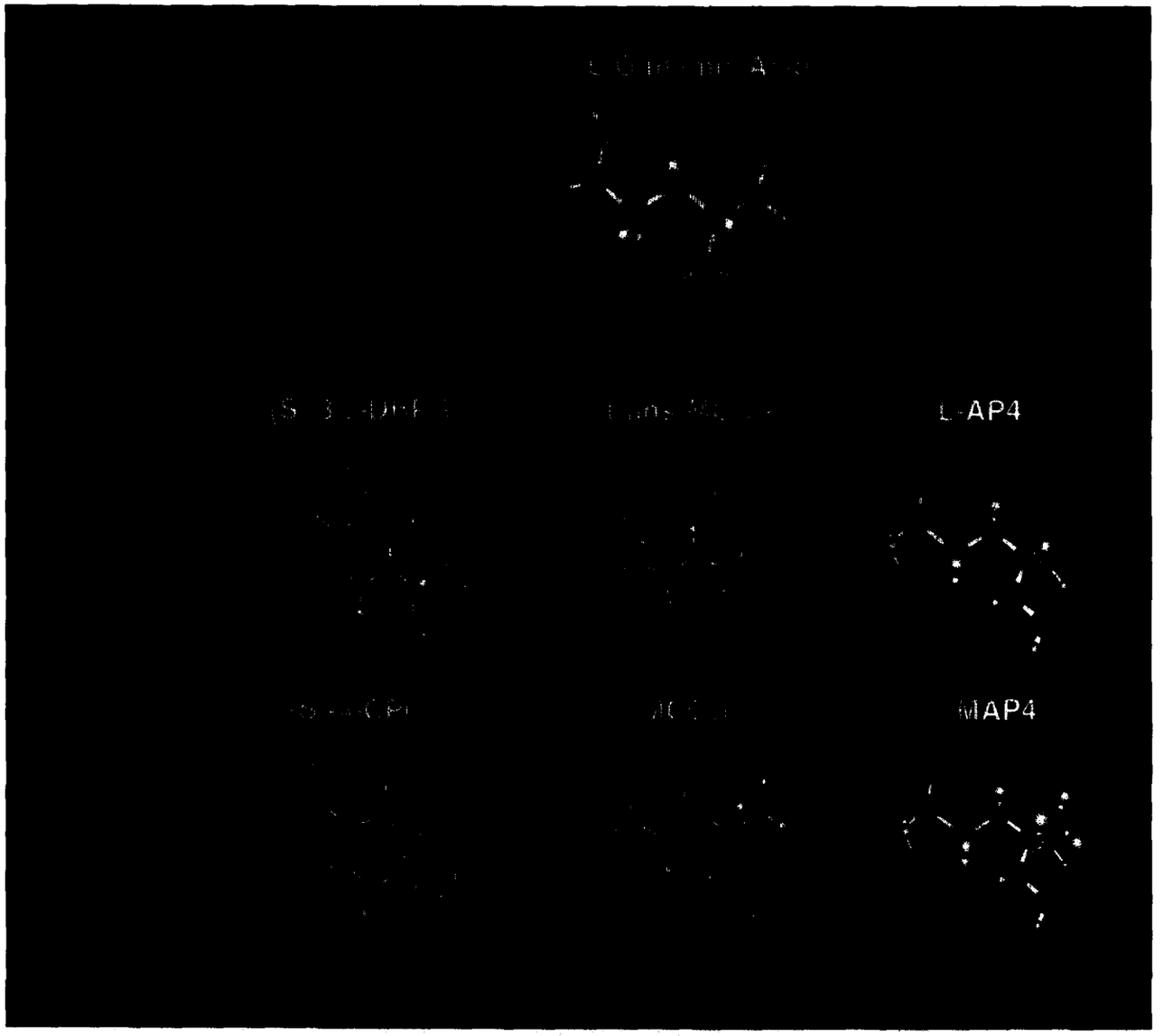


Figure 1. *Prototypic agonists and antagonists of each mGluR group. 3,5-DHPG, (S)-3,5-dihydroxyphenylglycine; (S)-4-CPG, (S)-4-carboxyphenylglycine;* trans*-MCG-I, (2S,1'S,2'R,3'R)-2-(2-carboxy-3-methoxymethylcyclopropyl)glycine; MCCG-I, α-methyl-carboxycyclopropylglycine; L-AP4, (S)-2-amino-4-phosphonobutyric acid; MAP4, α-methyl-2-amino-4-phosphonobutyric acid.*

derivatives have agonist and antagonist activity not only at group I but also at group II and group III mGluRs. The scheme illustrated in Figure 1 also does not reflect emerging evidence that subtypes within one group differ to some extent in their pharmacological properties:

- There are recent reports showing that the group I subtypes $mGluR_1$ and $mGluR_5$ exhibit a different pharmacology with respect to several phenylglycine antagonists[23,24].
- Quisqualate clearly activates $mGluR_3$ (Ref. 7) but is virtually inactive at $mGluR_2$ (Ref. 6), while glutamate is similarly potent at these two group II mGluRs.
- L-AP4 is significantly more potent than L-SOP at $mGluR_4$, while both compounds exhibit a comparable potency at $mGluR_7$ (Refs 11,20).

Given the structural similarity to glutamate of all known agonists and antagonists, it can be speculated that they are all competing for a glutamate-binding domain homologous within the mGluR subtypes. Currently, no clear examples of compounds acting at allosteric sites are known.

Effects on synaptic integration, transmission and plasticity

Like metabotropic receptors of other neurotransmitters, hormones and other cell regulators, mGluRs couple to G proteins and modulate second messenger levels as well as ion channel activity[25,26]. The classification of mGluRs into three groups, based on their functional properties at the molecular level, provides a general guideline for the description of their neurophysiological functions (Table 1).

Each mGluR subtype can potentially couple to different signal transduction mechanisms in different types of nerve cells. Activation of group I mGluRs most often results in membrane depolarization and/or increased excitability of nerve cells[27,28]. Furthermore, presynaptically localized group I mGluRs generally upregulate synaptic transmission. The underlying mechanisms include modulation of *N*-methyl-D-aspartate (NMDA) and 2-(aminomethyl)-aspartic acid (AMPA) receptor-mediated membrane currents, most likely through phosphorylation of the respective ion channels[29–31]. There is also indirect evidence that group I mGluRs enhance the amount of glutamate released during synaptic activity[32]. Although the above are short-term effects on synaptic transmission, evidence has accumulated that mGluRs are also involved in long-lasting regulation of synaptic efficacy, such as long-term potentiation and long-term depression of synaptic efficacy[33–38]. These phenomena serve as model systems for learning and memory and, accordingly, a role of mGluRs in these brain functions has been proposed[37–40].

Group II mGluRs depress release of glutamate[32] and γ-aminobutyric acid (GABA)[41] as well as glutamatergic[42-44] and GABAergic[45–47] synaptic transmission. This effect is thought to result from a modulation of presynaptic calcium channels[48–51].

Group III mGluRs mediate effects similar to those of group II mGluRs[42,52,53]. Although functionally similar, they exhibit different patterns of expression. Together with their preference for structurally distinct ligands, drugs acting at group III mGluRs target different neuronal systems.

Therapeutic potential of drugs acting at mGluRs

In the last decade a variety of disease states has become associated with disturbances in the activation of glutamate receptors. Historically, much attention has been given to the excessive activation of ionotropic glutamate receptors and the consequent disturbance in excitatory synaptic transmission and induction of calcium-mediated cell death. This concept was instrumental in the extensive search for antagonists of ionotropic glutamate receptors as potential drugs for therapeutic indications such as stroke and epilepsy. An extension of this concept emerged from the functional properties of mGluRs. Not only

Table 1. Typical effects of activation of each mGluR group on synaptic integration, transmission and plasticity

Tissue or function affected	Group I	Group II	Group III
Somatodendritic membrane	Depolarization, increased excitability[27,28]	Mostly no effect	Mostly no effect
Excitatory synaptic transmission	Mostly no effect, but also decrease[37] or increase[32]	Decrease[42–44]	Decrease[42,52,53]
Inhibitory synaptic transmission	No effect	Decrease[45–47]	?
Synaptic plasticity/ learning and memory	Supportive[33–40]	??	??

antagonists but also agonists of mGluRs interfere with a variety of pathophysiological processes, which are described below and summarized in Table 2.

Table 2. Putative therapeutic applications of mGluR agonists and antagonists

Therapeutic indication	Group I	Group II	Group III
Epilepsy	Antagonist[54–57]	Agonist[54–57]	Agonist[54]
Cerebral ischemia	Antagonist[59–61]	Agonist[61–63]	Agonist[61–63]
Chronic neurodegenerative diseases	Antagonist[59–61], agonist?[66,67]	Agonist[62–64]	Agonist[63]
Pain	Antagonist[68–72]	?	?
Spinal cord injury	Agonist?[73]	Agonist?[73]	?
Neuropsychiatric diseases	?	?	?

Epilepsy

The typical functional consequence of activation of group I mGluRs is an excitation or increased excitability of nerve cells, while group II/III mGluRs generally mediate a depression of synaptic transmission. Based on the premise that reduction of excitation or excitability is a useful therapeutic strategy for the treatment of epilepsy, antagonists for group I mGluRs and/or agonists for group II/III mGluRs are potentially antiepileptic. In accordance with this concept is the observation that injection of a selective agonist for group I mGluRs into the thalamus of mice induced limbic seizures, whereas group II and group III mGluR agonists reduced this epileptiform activity[54]. Furthermore, (+)-α–methyl-4-carboxyphenylglycine – a mixed group I and group II antagonist – suppressed spontaneous epileptiform activity induced by the $GABA_A$ antagonist bicuculline in the immature neocortex[55,56], and (*S*)-4-carboxy-3-hydroxyphenylglycine – an antagonist at $mGluR_{1a}$ receptors and an agonist at $mGluR_2$ – antagonized audiogenic convulsions in DBA/2 mice[57].

Cerebral ischemia

Excessive activity of glutamate can result in neuronal death – a pathophysiological process underlying the concept of excitotoxicity[58]. It is thought that loss of neuronal function consequent to cerebral hypoxia–ischemia results from, at least in part, such an excitotoxic mechanism. mGluRs appear to interfere with these processes in two different ways. Agonists and antagonists of group I mGluRs amplify and attenuate, respectively, neuronal death induced by excessive activation of ionotropic glutamate receptors or oxygen–glucose deprivation[59–61]. Furthermore, agonists at group II/III mGluRs exhibit neuroprotective properties[61–63].

Chronic neurodegenerative diseases

Chronic neurodegenerative diseases are associated with a heterogeneous group of pathophysiological processes, some of which are of major clinical importance. The pathophysiological processes overlap with those in ischemia. Remarkably, group II and group III agonists prevent cell death not only when induced by excessive activation of NMDA- or kainate-sensitive ionotropic glutamate receptors[62,63], but also by β-amyloid peptide[64]. Furthermore, recent studies have demonstrated that DCG-IV – a potent group II mGluR agonist – could still rescue a large proportion of cultured cortical neurons when applied 30 min after an otherwise excitotoxic dose of NMDA (Ref. 63). Such a 'delayed rescue' was also described for NMDA receptor antagonists[65], but group II agonists are clearly more effective, suggesting effects downstream to calcium-mediated cytotoxicity[63]. The role of group I mGluRs seems to be more complex. As described above, activity of group I mGluRs clearly potentiates acute excitotoxic damage of neurons. However, in order to survive, developing neurons seem to require some function mediated by $mGluR_5$ (Ref. 66). Furthermore, evidence has been provided that stimulation of group I mGluRs accelerates processing of amyloid precursor protein into soluble, non-amyloidogenic derivatives and might thus depress formation of senile plaques found in Alzheimer's disease[67].

Pain

There is emerging evidence that group I mGluRs are involved in transmission of noxious signals in the spinal cord[68–70]. Furthermore, at the level of the ventrobasal thalamus, responses to noxious sensory stimuli appear to be mediated or gated by $mGluR_1$ (Refs 71,72).

Spinal cord injury

The pathophysiology of spinal cord injury involves a primary mechanical lesion followed by a delayed secondary injury, probably resulting from glutamate- or calcium-mediated cytotoxicity. Recently, it has been proposed that astrocytes may exhibit mGluR-mediated neuroprotective properties following traumatic spinal cord injury[73].

Neuropsychiatric diseases

Pharmacotherapy of neuropsychiatric diseases relies to a large extent on drugs interacting with metabotropic receptors of transmitters other than glutamate. Since the signal

transduction mechanisms of mGluRs overlap with those of more classical 'neuromodulators', mGluR agonists and/or antagonists might have potential therapeutic applications in neuropsychiatric diseases.

Future perspectives

Intense research efforts during the last few years have revealed the involvement of mGluRs in many physiological and pathophysiological processes. Present knowledge clearly suggests that mGluRs are potential drug targets with a highly innovative potential. Further progress in drug discovery is expected along two main lines:

1. Medicinal chemists will aim at the discovery of novel, potent, subtype-specific and bioavailable compounds. The classical lead-finding and optimization processes will be facilitated by the availability of individual mGluR subtypes stably expressed in cell lines used for functional screening of compound libraries and profiling for SAR studies. Cellular assays have the capacity to detect not only competitive agonists and antagonists but also modulators of possible allosteric sites at mGluRs.

2. Physiologists and pharmacologists will continue to explore the therapeutic potential of modulating the activity of specific mGluR subtypes. These studies will not necessarily be dependent on the availability of optimal reference compounds, as modern molecular biological approaches, such as gene targeting and application of antisense oligonucleotides, provide complementary approaches.

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New therapeutic agents for the treatment of insulin resistance and NIDDM

Nicholas C. Turner

Two types of diabetes mellitus are recognized, type I insulin-dependent and type II non-insulin-dependent. Insulin-dependent diabetes mellitus is characterized by autoimmune pancreatic β-cell destruction and absolute dependence on exogenous insulin. The much more prevalent non-insulin-dependent variety is usually associated with hepatic and peripheral insulin resistance and impaired β-cell function. Current therapy of non-insulin-dependent diabetes mellitus is based on lifestyle and drug regimes that maintain blood glucose concentrations close to normal. Rapid advances have recently been made in two pharmacological strategies, thiazolidinedione insulin-sensitizing agents and thermogenic/antidiabetic β_3-adrenoceptor agonists.

Resistance to the metabolic actions of insulin is one of the salient features of impaired glucose tolerance and non-insulin-dependent diabetes (NIDDM). Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs (adipocytes and skeletal muscle) and by impaired inhibition of hepatic glucose output[1–8]. Under such conditions, normal glycaemic control is maintained only if the pancreatic β-cell can increase its capacity to secrete insulin to compensate for the extent of insulin resistance[1–8]. In many patients with impaired glucose tolerance, insulin resistance is, therefore, associated with hyperinsulinaemia[1–8]. The extent of impaired glucose tolerance varies, furthermore, as a function of insulin resistance and the capacity of the pancreas to maintain a compensatory hyperinsulinaemic state[6,7]. Indeed, the prevailing hyperinsulinaemia compensates for the profound insulin resistance and prevents the development of frank NIDDM.

It is generally agreed that insulin resistance in NIDDM is coupled to β-cell dysfunction and that it is the inability to maintain a hyperinsulinaemic state that leads to the development of hyperglycaemia[1–8]. NIDDM patients with frank hyperglycaemia are, however, rarely hypoinsulinaemic when compared to subjects with normal glucose tolerance[7]. The relative insulin deficiency and the failure of insulin to suppress hepatic glucose output results, nevertheless, in fasting hyperglycaemia; this, with the reduction in postprandial glucose utilization, causes severe glucose intolerance and sustained hyperglycaemia.

Whether insulin resistance or relative insulin deficiency is the primary defect in patients with NIDDM is a matter of some debate and has been discussed recently[7,8]. There is, however, general consensus that most patients with NIDDM are insulin-resistant. The existence of insulin resistance in non-diabetic, immediate relatives of patients with NIDDM and in non-diabetic patients who subsequently develop NIDDM (Refs 6–8) suggests, furthermore, that insulin resistance is the primary factor, and probably the driving factor, in the development of NIDDM.

Although the molecular mechanisms of insulin resistance are becoming better understood (Box 1), it is unclear why the

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