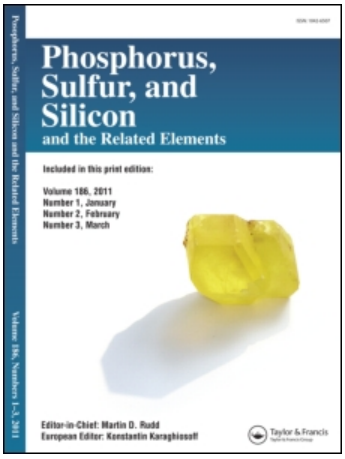


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# PHOSPHONO SUBSTITUTED AMINO ACIDS AS SELECTIVE METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

DAVID E. JANE[1]*, KAY PITTAWAY[2], DAVID C. SUNTER[2], NICOLA K. THOMAS[1] and HEONG-WAI TSE[1]
[1]Department of Pharmacology, School of Medical Sciences, Bristol, BS8 1TD, U.K. and [2]Tocris Cookson, Churchill Building, Langford House, Bristol, BS18 7DY, UK

Abstract New phosphono substituted amino acid antagonists have been prepared and used to discriminate between different types of presynaptic metabotropic glutamate receptors (mGluRs) in the neonatal rat spinal cord that are activated selectively by L-2-amino-4-phosphonobutanoate (L-AP4) and (1S,3S)-1-aminocyclopentane-1,3-dicarboxylate ((1S,3S)-ACPD). (RS)-α-Methyl-4-phosphonophenylglycine (MPPG; $K_D$ 9.2.μM), (S)-2-amino-2-methyl-4-phosphonobutanoate (MAP4; $K_D$ 22 μM) and (RS)-α-methylserine-O-phosphate (MSOP; $K_D$ 51 μM) were potent and selective antagonists of L-AP4-activated mGluRs. (RS)-α-Methyl-4-tetrazolylphenylglycine (MTPG; $K_D$ 77 μM) and (RS)-α-methylserine-O-phosphate monophenylphospho ester (MSOPPE; $K_D$ 73 μM) were moderately potent and preferential antagonists of (1S,3S)-ACPD-activated mGluRs. Structure-activity relationships are briefly discussed.

*Key Words:* metabotropic glutamate receptor (mGluR); mGluR antagonists; L-AP4; (1S,3S)-ACPD.



## INTRODUCTION

It is widely accepted that (S)-glutamate is the predominant excitatory transmitter in the central nervous system, acting at a range of ionotropic and metabotropic glutamate receptors (mGluRs). Ionotropic glutamate receptors mediate their effects via ligand gated ion-channels and can be sub-divided into three main types named after the specific agonists which activate them, the N-methyl-D-aspartate (NMDA), (RS)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors. Phosphono analogues of longer chain congenors of glutamate (particularly the R forms) are well

hydantoins in 6N HCl. MSOP and MSOPPE were synthesized by a variation on the method of Fölsch and Mellander starting with α-methylserine.[9]

## PHARMACOLOGY

The activity of the new compounds at reversing L-AP4- and (1S,3S)-ACPD-induced depression of the dorsal root-evoked monosynaptic excitation was investigated in the isolated hemisected neonatal rat spinal cord preparation.[5,6] These results together with apparent $K_D$ values for previously reported antagonists are summarized in Table 1.

TABLE 1 Apparent $K_D$ values for antagonism of test compounds of L-AP4- and (1S,3S)-ACPD sensitive presynaptic receptor sites in the neonatal rat spinal cord.

| COMPOUND | $K_D$ (μM) for antagonism of depression mediated by: | |
|---|---|---|
| | L-AP4 | (1S,3S)-ACPD |
| (+)-MCPG | 227 ± 12 (4) | 479 ± 37 (5) |
| (RS)-MTPG | 188 ± 9 (3) | 77.2 ± 7 (7) |
| (RS)-MPPG | 9.2 ± 0.3 (9) | 113 ± 13 (3) |
| (S)-MAP4 | 22 ± 5 (5) | > 500 |
| (RS)-MSOP | 51 ± 6 (3) | > 700 (3) |
| (RS)-MSOPPE | 221 ± 17 (3) | 73 ± 3 (3) |

The mGluR antagonists described above have no effect on postsynaptic mGluRs and only weak and variable effects on postsynaptic ionotropic receptors such as NMDA and AMPA receptors.

## DISCUSSION

L-AP4-activated receptors were most potently antagonized by MPPG, which was also reasonably selective for these receptors, but less specific than (S)-MAP4 and (RS)-MSOP. MTPG and MSOPPE were somewhat selective for (1S,3S)-ACPD-activated mGluRs. The results indicate that both the open-chain and phenyl-spaced analogues can interact with the same sites on the L-AP4-sensitive receptor. The fact that MSOPPE is more selective for the (1S,3S)-ACPD activated receptor suggests that either two hydroxyl groups are necessary for interaction with the L-AP4 activated receptor, or that the O-phenyl group is too large and interferes with receptor interaction, or a combination

known as specific antagonists at the NMDA receptor[1] and together with antagonists of the AMPA/kainate receptors have received much attention as potential therapeutic drugs in a range of disease states including, traumatic head and spinal injury, stroke, epilepsy, spasticity, Parkinson's disease and Huntington's disease.[2]

In recent years the structure and function of mGluRs has come under intense investigation.[3,4] To date, molecular biologists have identified eight mGluRs which when expressed couple to second messenger systems through G proteins.[3,4] Group I receptors (mGluRs 1/5) are positively coupled to phospholipase C activity while group II (mGluRs 2/3) and group III (mGluRs 4/6-8) receptors are negatively coupled to adenyl cyclase activity. Recently the antagonist action of novel phenylglycine analogues on mGluRs has been reviewed.[4] The actions of (RS)-α-methyl-4-carboxyphenylglycine (MCPG), the first mGluR antagonist, were reported to be relatively non-specific for particular mGluR sub-types and therefore new analogues have been developed. To this end we recently reported the actions of (S)-2-amino-2-methyl-4-phosphonobutanoate (MAP4) and (2S,1'S,2'S)-2-(2-carboxycyclopropyl)alanine (MCCG) which are selective antagonists for different presynaptically located mGluRs that are activated specifically by L-2-amino-4-phosphonobutanoate (L-AP4) and (1S,3S)-1-aminocyclopentane-1,3-dicarboxylate ((1S,3S)-ACPD).[5] These mGluRs are considered to correspond to one or more receptors within group III and group II, respectively.[4] We have now developed new phenylglycine and open chain analogues of MCPG and MAP4, including (RS)-α-methyl-4-phosphonophenylglycine (MPPG), (RS)-α-methyl-4-tetrazolylphenylglycine (MTPG),[6] (RS)-α-methylserine-O-phosphate (MSOP) and (RS)-α-methylserine-O-phosphate monophenylphospho ester (MSOPPE), and compared their actions in neonatal rat spinal cord with those of the presynaptic mGluR antagonists previously reported.



## CHEMISTRY

(S)-MAP4 was prepared by reaction of diethyl 2-bromoethylphosphonate and the cuprate derived from 5-lithio-(2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methyl-pyrazine,[7] followed by hydrolysis of the intermediate firstly in 1N TFA in THF and then 6N HCl. (RS)-MTPG and (RS)-MPPG were synthesized by Bucherer-Berg reaction[8] on the appropriately substituted acetophenones followed by hydrolysis of the intermediate

of these factors. In contrast, the (1S,3S)-ACPD sensitive mGluR accommodates the O-phenyl group of MSOPPE suggesting that a) only one hydroxyl is necessary for receptor interaction and b) there may be a fairly large hydrophobic cavity in the receptor that the phenyl group can interact with. Using structural requirements for antagonism of the L-AP4 and (1S,3S)-ACPD activated receptors revealed in this and earlier studies it should be possible to design more potent and selective antagonists. Molecular modelling studies aimed at defining antagonist pharmacophores for these receptors are in progress and these, together with an on-going synthetic programme should lead to even more potent and selective mGluR antagonists in the future.

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