The Methylglutamate, SYM 2081, is a Potent and Highly Selective Agonist at Kainate Receptors

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ABSTRACT
The methylglutamate analog (2S,4R)-4-methylglutamate (SYM 2081) has been shown to potently displace high affinity [3H]kainate binding to cortical tissue and to recombinant kainate receptors, and to evoke rapidly desensitizing responses in electrophysiological recordings. We have used two electrode voltage clamp recordings to compare the potency and efficacy of SYM 2081 with other a-aminooxy-5-methyl-4-isoxazole-propionate (AMPA)/kainate receptor agonists at homomeric kainate and AMPA receptors expressed in Xenopus oocytes. In the presence of concanavalin A to reduce agonist induced desensitization at kainate receptors, SYM 2081 was a potent agonist at homomeric kainate receptors composed of the GluR5 and GluR6 subunit, with an EC50 of 0.12 ± 0.02 and 0.23 ± 0.01 μM, respectively. SYM 2081 was highly selective for kainate receptors, the EC50 for activation of AMPA receptors composed of the GluR1 and GluR3 subunits was 132 ± 44 and 453 ± 57 μM, respectively. Other methylglutamate analogs were tested for kainate receptor agonist activity. Methylglutamate compounds with the methyl group at the 2 or 3 position of glutamate were inactive indicating that positioning of the methyl group at the 4 position was essential for agonist activity. Of the four stereoisomers of 4-methylglutamate, SYM 2081 (2S,4R) was the most potent agonist. The (2R,4R) isomer was estimated to be 20-fold and the (2S,4S)-isomer approximately 1000-fold less potent than SYM 2081. These results indicate that SYM 2081 is a potent and selective agonist at kainate receptors, and thus will be a useful ligand for evaluating the role of kainate receptors in central nervous system function and disease.

In addition to its role in synaptic transmission, the excitatory amino acid neurotransmitter Glu has been implicated in the pathophysiology of epilepsy, stroke and a number of neurodegenerative syndromes including amyotrophic lateral sclerosis (Choi, 1988; Rogawski, 1995; Smith and Appel, 1995). The ionotropic GluR family has traditionally been classified into three broad subtypes based on pharmacological and electrophysiological properties into NMDA, AMPA and KA receptors (Collingridge and Lester, 1989; Lodge, 1997; Monaghan et al., 1989). The distinction of two subtypes of non-NMDA receptors was supported by initial binding studies showing high affinity kainate binding sites that differed from those labeled by AMPA (reviewed in Monaghan et al., 1989). This distinction was later supported by cloning studies. Although these studies have revealed a far greater number of ionotropic glutamate receptor subunits than initially expected, the subunits can be grouped into NMDA, AMPA and kainate receptor subfamilies based on sequence homology and pharmacological properties (Hollmann and Heinemann, 1994; Seeburg, 1993). Non-NMDA (AMPA and KA) ionotropic receptors are defined by at least nine cloned subunits that have been grouped according to their relatively high sequence identity and similar pharmacology. GluR1-4 subunits compose the AMPA receptor subfamily, while GluR5-7 compose the kainate receptor subfamily (Bettler et al., 1990; Egebjerg et al., 1991; Bettler et al., 1992; Lomeli et al., 1992). Two additional subunits have been cloned, KA1 and KA2, which form nonfunctional high affinity kainate binding sites, but combine with and alter the functional properties of GluR5 and GluR6 (Werner et al., 1991; Herb et al., 1992; Sakimura et al., 1992).

An appreciation of the role of NMDA and AMPA receptors in normal and pathophysiologic central nervous system function has been aided by the availability of relatively selective agonists and antagonists. However, the role of kainate receptors in the central nervous system is not well understood. In part, this is due to the lack of selective agonists and antagonists, which can differentiate kainate from AMPA receptors. Thus, to date, the most selective antagonist, NS102 shows only 20-fold selectivity for kainate receptors over AMPA receptors (Verdoorn et al., 1994; Wilding and Huettner, 1996).

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ABBREVIATIONS: AMPA, a-aminooxy-3-hydroxy-5-methyl-4-isoxazole-propionate; Glu, glutamate; GluR, glutamate receptor; KA, kainate; NMDA, N-methyl-D-aspartate; SYM 2081, (2S,4R)-4-methylglutamate.
In addition, agonists such as kainate and domoate show only limited selectivity for kainate receptors and also activate AMPA receptors (Hollmann and Heinemann, 1994). Moreover, the current responses evoked by these agonists at AMPA receptors are nondesensitizing which further limits the use of these agonists to selectively activate kainate receptors.

Recently, four stereoisomers of 4-methylglutamate have been synthesized and initial studies showed that the (2S,4R) stereoisomer (SYM 2081) was able to displace kainate binding to high affinity [3H]kainate binding sites with relatively high potency, comparable to that of kainate itself, which likely represents binding to kainate receptors (Gu et al., 1995). Moreover, recent studies have demonstrated that at low concentrations SYM 2081 reduces kainate evoked responses in recordings from recombinant kainate receptors composed of the GluR6 subunit by inducing desensitization. At higher concentrations, SYM 2081 produces a rapidly desensitizing current response similar to that evoked by kainate (Zhou et al., 1997). In our studies we have characterized the agonist properties of SYM 2081 at recombinant AMPA and kainate receptors expressed in Xenopus oocytes and compared it with the selectivity of other AMPA/kainate receptor ligands for kainate receptors. We find that SYM 2081 is a potent and selective agonist at kainate receptors showing 500- to 2000-fold selectivity for homomeric kainate receptors composed of GluR5 and GluR6 subunits over AMPA receptor components of GluR1, GluR2 or GluR3 subunits. The location of the methyl group at the 4 position of glutamate is critical for kainate receptor agonist activity as glutamate analogs with the methyl group at the 2 or 3 position had negligible activity.

**Methods**

cDNA plasmids. GluR1flp, GluR3flp, GluR6(Q) and GluR6(R) cDNA in pBluescript were gifts from Dr. S. Heinemann (Salk Institute, La Jolla, CA), while GluR5-2a(Q), in CMV expression vector, was provided by Dr. P. Seeburg (Department of Molecular Neurobiology, Max Planck Institute, Heidelberg, Germany).

*Xenopus oocyte injections.* Oocytes were removed from *Xenopus laevis* frogs anesthetized by immersion in .2% tricaine for 15 to 30 min. Harvested ovarian lobes were defolliculated by incubation in 2 mg/ml of collagenase (type IA, Sigma Chemical Co., St. Louis, MO) for 2 hr at room temperature on an orbital shaker in calcium-free ND-96 solution containing in mM: 96 NaCl, 2 KCl, 1 MgCl2 and 5 HEPES (pH 7.4). The oocytes were rinsed five to six times with a Barth’s solution that contained (in mM): 88 NaCl, 1 KCl, 0.41 CaCl2, .33 Ca(N03)2, 1 MgSO4, 2.4 NaHCO3 and 10 HEPES (pH = 7.4), and selected stage V-VI oocytes were stored at 18°C in Barth’s solution supplemented with 1 mM Na-Pyruvate, .01 mg/ml gentamycin and 500- to 2000-fold selectivity for homomeric kainate receptors.

Results

As shown in figure 1A, oocytes expressing GluR6 subunits showed inward current responses to 30 μM kainate. After incubation of the oocyte in concanavalin A (0.3 mg/ml), the subsequent kainate response was markedly potentiated, such that desensitization was almost completely eliminated. Similar current responses were observed with 10 μM SYM 2081, although the response in the absence and presence of concanavalin A tended to be larger than the response to kainate. The graph in figure 1B plots the current response to SYM 2081 producing a measurable current response at 30 nM kainate. SYM 2081 evoked a measurable current response at 30 nM kainate.

**Electrophysiology.** Electrophysiological recordings were performed 3 to 10 days after injection and were carried out at room temperature in a control ringer solutions containing in mM: 115 NaCl, 2.5 KCl, 1.0 BaCl2 and 10 HEPES (pH = 7.4). Two electrode voltage clamp recordings were obtained with a Geneclamp amplifier (Axon Instruments, Burlingame, CA) using 3 mM KCl-filled microelectrodes (1-5 MΩ). Recordings were carried out at a holding potential of -60 mV unless otherwise noted. In most cases, before recording the oocytes were incubated in 0.3 mg/ml concanavalin A (Type IV, Sigma) for 5 to 10 min to prevent rapid desensitization of agonist responses. In studies characterizing the potency of SYM 2081 injected into the GluR1 and GluR2 subunits (1:2 ratio), heteromeric receptor formation was confirmed with the demonstration of outwardly rectifying responses to 1 mM kainate.

**Data analysis.** Concentration-effect data were fit to the logistic equation:

\[
I = I_{\text{max}}/(1 + ([\text{agonist}]/EC_{50})^{nH})
\]

where \(I_{\text{max}}\) is the maximal current, \([\text{agonist}]\) is the concentration, \(EC_{50}\) is the concentration of agonist resulting in half maximal activation and \(nH\) is an empirical parameter describing the steepness of fit and having the same meaning as the Hill coefficient. NFIT (Iland Products, Galveston, TX) was used for nonlinear curve fitting. Data are presented as the mean ± S.E.M.; n is the number of oocytes tested. Differences between means were compared with a paired Student’s t test.

**Drugs.** The stereoisomers of methylglutamate and domoic acid were obtained from Tocris Cookson (St. Louis, MO). All other drugs and chemicals were obtained from Sigma.

**SYM 2081 potency and selectivity.** The potency of SYM 2081 at activating homomeric kainate receptors composed of GluR5 and GluR6 subunits was assessed in oocytes pretreated with concanavalin A to prevent desensitization, as discussed previously. The traces in figure 2A (top panel) are from an oocyte expressing the GluR6 subunit and show that SYM 2081 evoked a measurable current response at 30 nM that was saturating at 1 to 3 μM. The current response relationship for this oocyte and several others are summa-
rized in the graph in figure 2B. The EC\textsubscript{50} for SYM 2081 activation of GluR6 was 0.23 ± 0.01 μM. Similar concentration dependent currents were evoked by SYM 2081 in oocytes expressing the GluR5(Q) subunit (fig. 2B) and SYM 2081 showed similar potency at this kainate receptor subtype (table 1). To determine the specificity of SYM 2081 for kainate receptors similar studies were carried out in homomeric AMPA receptors expressing the GluR1 or GluR3 subunits and heteromeric receptors containing the GluR1 and GluR2 subunits. As shown in the current traces in figure 2A (bottom panel) SYM 2081 evoked inward current responses in an oocyte expressing the GluR1 subunit. However, this was at concentrations considerably higher than those required to activate kainate receptor responses. The EC\textsubscript{50} for SYM 2081 activation of oocytes expressing homomeric AMPA receptors composed of the GluR1, or GluR3 subunits was 132 ± 44 and 453 ± 57 μM, respectively (fig. 2B; table 1). In addition, as most AMPA receptors in situ likely contain the GluR2 subunit, a heteromeric AMPA receptor containing the GluR2 subunit was also tested. The EC\textsubscript{50} for SYM 2081 activation of oocytes expressing heteromeric receptors composed of GluR1 and GluR2 subunits was 293 ± 17 μM (n = 5). Thus, SYM 2081 is an extremely selective agonist at kainate receptors being almost 1500-fold more potent at kainate receptors than AMPA receptors.

To compare the selectivity of SYM 2081 with other commonly used agonists at AMPA and kainate receptors, a similar series of experiments were conducted looking at the relative potency of domoate, kainate and glutamate for activation of kainate and AMPA receptors expressed in the oocyte system. Domoate was the most potent agonist tested at kainate receptors, roughly 2- to 3-fold more potent than SYM 2081. However, it was also relatively potent at AMPA receptors, particularly those composed of the GluR1 subunit (fig. 3; table 1).

### Table 1

<table>
<thead>
<tr>
<th>Agonist</th>
<th>GluR6</th>
<th>GluR5</th>
<th>GluR3</th>
<th>GluR1</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYM</td>
<td>453 ± 5.7</td>
<td>0.7 ± 0.1</td>
<td>5</td>
<td>132 ± 44</td>
</tr>
<tr>
<td>Domoate</td>
<td>21 ± 2.3</td>
<td>1.2 ± 0.1</td>
<td>5</td>
<td>0.97 ± 0.12</td>
</tr>
<tr>
<td>Kainate</td>
<td>69.6 ± 5.5</td>
<td>1.1 ± 0.1</td>
<td>5</td>
<td>46.9 ± 3.5</td>
</tr>
<tr>
<td>Glutamate</td>
<td>16.2 ± 1.9</td>
<td>1.1 ± 0.1</td>
<td>5</td>
<td>9.1 ± 0.4</td>
</tr>
</tbody>
</table>

*Numbers are mean ± S.E.M.

*The selectivity ratio is calculated as the ratio of the agonist EC\textsubscript{50} at AMPA receptors to agonist EC\textsubscript{50} at kainate receptors, where the EC\textsubscript{50} values are the average of EC\textsubscript{50} at GluR1 and GluR3, and GluR5 and GluR6, respectively.
were obtained in the absence and presence of 100 μM cyclothiazide. This subunit was chosen as it had higher affinity for SYM 2081, thus saturating concentrations could be used. In the absence of cyclothiazide, kainate (1 mM) evoked the largest steady state current, followed by domoate (100 μM), glutamate (1 mM) and SYM 2081 (3 mM) (fig. 4A, lower traces). The currents evoked by SYM 2081 were significantly smaller than the currents evoked by the other three agonists (P < .01). In the presence of cyclothiazide, at concentrations (100 μM) shown to eliminate glutamate desensitization at GluR1, the current evoked by saturating concentrations of SYM 2081 was similar to those evoked by domoate, kainate and significantly smaller (P < .01) than the current evoked by glutamate (fig. 4B, lower panel).

**Methylglutamate analog activity.** We also tested other commercially available stereoisomers of 4-methylglutamate and glutamate analogs with the methyl group the 2 or 3 position of glutamate for agonist activity at GluR6 (fig. 5A). Methylglutamate analogs with the methyl group at the 2 or 3 position had negligible agonist activity at the concentrations tested (100 μM) (see legend for description of agonists), indicating that positioning of the methyl group at the 4 position of glutamate is critical for agonist activity at the kainate receptor. The racemates of (±)-threo-4-methylglutamate [(2R,4R):(2S,4S)] and (±)-erythro-4-methylglutamate [(2R,4S):(2S,4R)] had significant activity when compared with SYM 2081 (2S,4R). The agonist-like activity of (±)-erythro-4-methylglutamate likely results from the (2S, 4R) isomer (i.e., SYM 2081) within the racemic mixture as 300 nM of the racemic mixture (which would contain 150 nM of each isomer) evoked a current response identical to that evoked by 150 nM of the (2S,4R) isomer (SYM 2081) alone (data not shown), and not a larger current, which one would expect if both isomers had full activity.

The relatively potent agonist activity of the (±)-threo-4-methylglutamate likely results from the (2R,4R) isomer as the (2S,4S) isomer of (±)-threo-4-methylglutamate had minimal effect at 100 μM. The agonist potency of (±)-threo-4-methylglutamate was characterized more fully in concentration response studies in oocytes expressing GluR6 subunits. The EC50 for activation of kainate receptor current responses was 13.4 μM. Given that the (2S,4S) produces negligible current responses at this concentration one would assume that the activity of the 1:1 racemate mixture is due to the activity of the (2R,4R) isomer alone. Thus, the EC50 for the (2R,4R) isomer is approximately 6 μM. To determine whether the (2S,4S) isomer acted as a weak or partial agonist, the current evoked by a high concentration of the (2S,4S) isomer was compared with that evoked by a saturating concentration of SYM 2081. The current response evoked by 3 mM of the (2S,4S) isomer (SYM 2081) alone (data not shown) and not a larger current, which one would expect if both isomers had full activity.

Although the inactive methylglutamate analogs lack agonist activity they may have competitive antagonist properties. This was examined by comparing the kainate response in the absence and presence of the methylglutamate analogs. In three oocytes expressing GluR6 subunits, 100 μM (2S)-α-methylglutamate, (±)-erythro-3-methylglutamate and (±)-threo-3-methylglutamate, had no effect on the kainate- (30 μM) evoked current response and were 96, 95 and 98% of control, respectively.
Initial binding studies demonstrated that SYM 2081 was a potent inhibitor of [³H]kainate binding to cortical tissue (Ghu et al., 1995). As high affinity kainate binding likely represents binding to kainate receptors this suggested an interaction of SYM 2081 with kainate receptors. This was confirmed in a more recent study in which SYM 2081 displaced kainate binding to recombinant GluR6 receptors, and elicited rapidly desensitizing current responses in electrophysiological studies with these same receptors (Zhou et al., 1997). In the present study the agonist activity of SYM 2081 was more fully characterized in two electrode, voltage clamp, recordings from kainate and AMPA receptors expressed in Xenopus oocytes and have compared it to other agonists at kainate and AMPA receptors. These studies demonstrate that SYM 2081 is a relatively potent agonist at kainate receptors and, furthermore, is the most selective kainate receptor agonist currently available, showing favorable selectivity for kainate receptors over AMPA receptors. In the presence of concanavalin A to reduce kainate receptor desensitization SYM 2081 evoked reliable kainate receptor current responses at low nanomolar concentrations (≥10 nM). However, much higher concentrations of the agonist were required to evoke reliable current responses at AMPA receptors. The ratio of the AMPA receptor EC₅₀ (mean of EC₅₀ at GluR1 and GluR3) to kainate receptor EC₅₀ (mean of EC₅₀ at GluR5 and GluR6) was used as an index of the relative selectivity of SYM 2081 for kainate receptors. Accordingly, SYM 2081 showed a 1500-fold selectivity for kainate receptors. Although domoic acid is an extremely potent agonist at kainate receptors, it is also active at AMPA receptors, particularly those composed of the GluR1 subunit and thus this limits its use as a kainate receptor specific agonist. Kainate showed similar limited selectivity for kainate receptors.

Other methylglutamate analogs were tested for agonist activity at kainate receptors and it would appear that the location of the methyl group at the 4 position of glutamate is critical for agonist activity. Thus, analogs with the methyl group at the 2 or 3 position on glutamate had little agonist activity at GluR6. Previous studies have compared the ability of the four different stereoisomers of 4-methylglutamate to displace high affinity kainate binding (Gu et al., 1995). These binding studies showed that the (2S,4R) isomer (SYM 2081) was the most potent at displacing [³H]kainate binding. The (2S,4S) and (2R,4R) isomers were 10-fold less potent, while the (2S,4R) stereoisomer was approximately 20- to 30-fold less potent than SYM 2081. As binding studies do not discriminate agonists from antagonists it was important to examine the activity of these other stereoisomers for agonist and antagonist activity using the more direct electrophysiological approach with a defined receptor population. Although not all isomers were available for the present study, an estimate of the different isomer activity could be obtained using a subtractive approach. As observed in binding studies, the isomers did show differences in agonist activity. The agonist activity of the (2R,4S) isomer is difficult to determine from studies with the racemic mixture of the erythro ([2R,4S]: (2S,4R)] isomers. It is possible that at high concentrations the (2R,4S)-isomer may act as a competitive antagonist or weak partial agonist, as the currents evoked by 100 μM of the racemic mixture of the erythro isomers (which would contain 50 μM SYM 2081) were smaller than those evoked by 10 μM SYM 2081. However, currents evoked by 300 nM of the racemic mixture (which would contain 150 nM of each isomer)
were identical to the currents evoked by 150 nM SYM 2081 [(2S,4R)-isomer] suggesting that the (2R,4S)-isomer has negligible agonist or antagonist activity at this low concentration. Recent studies with the individual isomers of (±)-erythro-4-methylglutamate have demonstrated that the (2R,4S)-isomer has agonist activity, albeit at much higher concentrations compared with SYM 2081 (Jones et al., 1997).

The racemic mixture of the threo-isomers of 4-methylglutamate [(2S,4S):(2R,4R)] had significant agonist activity. The EC_{50} for the threo isomers was approximately 13 μM. As (2S,4S) produces negligible current response at this low concentration, the agonist activity of the 1:1 mixture of the threo isomers lies solely in the (2R,4R) isomer, and thus the EC_{50} for the (2R,4R) isomer is approximately 6.5 μM. The roughly 30-fold separation in potency between the (2S,4R) and (2R,4R) isomers determined in these electrophysiological studies agrees quite well with the 10-fold separation observed in the binding studies (Gu et al., 1995). The kainate binding studies (Gu et al., 1995) have demonstrated that the (2S,4S) and (2R,4R) isomers show similar potency. In contrast, in the present studies they appear to be quite different, with the (2R,4R) isomer being a far more potent agonist at GluR6 than the (2S,4S) isomer. Binding studies cannot distinguish agonist vs. antagonist versus partial agonist activity, thus the discrepancy in activity of the (2R,4R) and (2S,4S) isomers among the two studies may indicate that the (2S,4S)-isomer possesses antagonist or partial agonist properties. At high concentrations the current response evoked by (2S,4S) was similar to the current response evoked by saturating concentrations of SYM 2081, indicating that the (2S,4S) isomer is a full, but weak, agonist. At this point the differences between binding and electrophysiological studies are unclear. It may be that the binding studies may reflect binding to a high affinity desensitized state or conformation as opposed to a channel opening state or conformation, i.e., the (2S,4S)-isomer may bind with high affinity to induce desensitization, compared with that necessary to produce activation. In support of this possibility, Jones et al. (1997) have observed that the IC_{50} for desensitization-induced inhibition of kainate responses were similar for the (2S,4S) and (2R,4R) isomer. It will be important to examine the erythro-isomer potency at kainate receptors using the individual isomers, as opposed to the subtractive approach used in the present studies. None the less, it is clear that the stereochemical configuration of 4-methylglutamate plays an important role in determining the affinity of methylglutamate for kainate receptors in both the binding studies and the more direct electrophysiological assays carried out in our study.

The relative efficacy of the different glutamate receptor ligands including SYM 2081 at kainate and AMPA receptors were compared. At kainate receptors composed of the GluR6 subunit, the current response to saturating concentrations of domoate was almost twice as large as those to kainate suggesting that kainate may be a partial agonist at kainate receptors composed of this subunit. The maximal response to SYM 2081 was 30% larger than the kainate response and the glutamate response was somewhat smaller. Thus, there appear to be differences in agonist efficacy in oocytes expressing the GluR6 subunit. At kainate receptors composed of the GluR5 subunit, the relative efficacy of kainate and domoate were similar as expected from studies with kainate receptors expressed by dorsal root ganglion neurons (Huettner, 1990). SYM 2081 showed similar efficacy to these agonists. At GluR1-containing AMPA receptors agonist efficacy was compared in the absence and presence of cyclothiazide. In the absence of cyclothiazide kainate evoked the largest maximal response followed by domoate, glutamate and then SYM 2081. This may in part reflect agonist induced desensitization. In the presence of cyclothiazide to eliminate AMPA receptor desensitization (Yamada and Tang, 1993; Patneau et al., 1993), glutamate was the most efficacious, and domoate, kainate and SYM 2081 were equally and somewhat less efficacious than glutamate.

In previous studies, it has been shown that at low nanomolar levels (below that at which it evokes current responses) SYM 2081 reduces kainate receptor responses
through an agonist-induced, desensitization-dependent, mechanism (Zhou et al., 1997; Wilding and Huetter, 1997). On the basis of these observations it was suggested that SYM 2081 may be useful as a kainate receptor antagonist (Zhou et al., 1997). Similar observations have been seen with glutamate at AMPA/kainate receptors (Trussel and Fishbach, 1989; Raman and Trussel, 1992), whereby at low concentrations, glutamate inhibited the subsequent peak response to a high concentration of glutamate. In these studies the EC_{50} for glutamate activation was 2 mM and the IC_{50} for desensitization-induced inhibition of the peak glutamate responses was 5 μM, a 400-fold separation between inhibition and activation. Similarly, at GluR6 receptors expressed in HEK 293 cells, glutamate shows an approximately 1500-fold separation between inhibition and activation (Heckmann et al., 1996). The IC_{50} concentration for SYM 2081 inhibition of kainate responses was determined to be 8 nM (Jones et al., 1997). In our study the EC_{50} for activation was determined to be approximately 200 nM; however, this was obtained in the presence of concanavalin A. In the absence of concanavalin A, the EC_{50} for activation of the peak desensitizing current responses in HEK 293 cells was determined to be 1 μM (Zhou et al., 1997; Jones et al., 1997). If one compares the concentrations of SYM 2081 required for inhibition with those necessary for activation one sees only a 125-fold separation between inhibition and activation. As glutamate is commonly used as an agonist at AMPA/kainate receptors, and given that SYM 2081 shows similar or even less separation between inhibitory and excitatory effects, the interpretation of the actions of SYM at kainate receptors with respect to its functional effects in vivo and in vitro will require careful consideration.

Thus, SYM 2081 has a number of features that will make it an extremely useful tool for the elucidation of the physiological role of kainate receptors: 1) it is a relatively potent agonist at kainate receptors; 2) it shows strong selectivity for kainate receptors over AMPA receptors; 3) it is as, or more, efficacious than kainate or glutamate at kainate receptors and finally 4) in the absence of cyclothiazide it appears to be much less efficacious than glutamate or kainate at AMPA receptors. These features should SYM 2081 useful ligand for evaluating the functional roles of the kainate receptor in central nervous system function and neurological disease.

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