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Editorial

Metabotropic glutamate receptors

It has been over 45 years since the excitatory and neurotoxic actions of glutamate were initially described. It was another two to three decades (1980s) until it was generally accepted that these effects were mediated via pharmacologically distinct receptors which were synaptically activated by endogenous glutamate (Watkins, 2000). Glutamatergic neuronal transmission was shown to involve the opening of sodium/calcium permeable ligand-gated ion channels that were pharmacologically distinguished as NMDA and non-NMDA (later know as quisqualate/AMPA and kainate) receptor subtypes. In addition to the role of these glutamate receptors in physiological processes such as fast-synaptic transmission and synaptic plasticity, the evidence for altered glutamatergic function in pathological processes was particularly compelling. The field now held tremendous promise as drugs that blocked NMDA or AMPA/kainate receptors were shown to be anticonvulsant and neuroprotective in animal models of ischemic and traumatic injury. Rightfully so, a large contingent of the glutamate field for the past decade has been focused on further elucidating the functional roles and properties of ionotropic receptors, and importantly, finding new antagonist drugs to treat these clinical conditions (Parsons et al., 1998).

However, while the majority of the glutamatergic field was diligently working on the above, another area of glutamate research was slowing emerging. In the mid-1980s, it was reported that glutamate can also activate so-called metabotropic or G-protein/second messenger coupled receptors. Metabotropic glutamate (mGlu) receptors were initially characterized as being coupled to the mobilization of intracellular calcium via the activation of phospholipase C (or phosphoinositide hydrolysis pathway). These mGlu receptors were pharmacologically distinguished from ionotropic glutamate receptors in that they were activated by quisqualate, but not AMPA (leading to the renaming of ionotropic quisqualate receptors to AMPA receptors). Importantly, in 1989, the mGlu selective agonist compound (*trans*- or 1*S*,3*R*-ACPD) was initially described. The discovery of 1*S*,3*R*-ACPD allowed researchers to selectively activate mGlu receptors, and clearly study for the first time their functions in vitro and in vivo. It was clear from these early studies that mGlu receptors, although they did not directly participate in fast-synaptic transmission, were important modulators of brain excitability and plasticity (Schoepp and Conn, 1993).

In 1991, two groups independently reported the expression cloning of the rat mGlu1 receptor subtype. This rapidly led to the cloning of multiple family members, which were subclassified into three different groups based on structural homologies, coupling mechanisms, and shared pharmacology (Nakanishi, 1992). At present, eight members of the mGlu receptor family (mGlu1–8) and a number of splice variants of certain subtypes have now been cloned from murine, rat, and human species (Pin and Duvoisin, 1995; Schoepp, 2001). Group I mGlu receptors, which include mGlu1 and mGlu5, are coupled via Gq to activation of phospholipase C and activated selectively by (*S*)3,5-dihydroxyphenyl glycine. Group II mGlu receptors (mGlu2 and mGlu3) are coupled via Gi/o to inhibition of adenylate cyclase and are selectively activated by agents such as 2*R*,4*R*-APDC, LY354740, and LY379268. Group III mGlu receptors (mGlu4, mGlu6, mGlu7, and mGlu8) are also coupled via Gi/o to inhibition of adenylate cyclase, but are selectively activated by the agonists L-amino-4-phosphonobutanoic acid (Schoepp et al., 1999). The mGlu receptors are members of the Type 3 GPCRs, which also include $GABA_B$, calcium-sensing, and certain pheromone receptors (Bockaert and Pin, 1999). With the cloning of mGlu receptor subtypes, the pharmacology of mGlu receptors began to progress more rapidly. Previously discovered and newly discovered mGlu receptor active agents could be fully characterized for their affinities and intrinsic activities across the cloned mGlu receptors. A number of potent and selective compounds for subtypes as well as subgroups of mGlu receptors have been discovered as useful radioligands or pharmacological tools to explore the biochemical and behavioral consequences of mGlu receptor modulation. The use of cloned mGlu receptors for high-throughput screens has also produced novel allosteric antagonists and potentiators for specific mGlu receptor subtypes (e.g., CPCCOEt and MPEP) (Varney and Suto, 2000). These compounds represent novel prototypic agents that can now be used to explore therapeutic applications in animal models.

In this special issue of *Pharmacology, Biochemistry and Behavior*, we have collected a wide range of original research reports that have in common the subject of mGlu receptors. These articles cover a range of topics which enhances our

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current understanding of mGlu receptor functions at the cellular, synaptic, regional, and whole animal levels. It is clear from the studies in this special issue that clinical studies with a variety of different mGlu receptor active ligands are just on the horizon. It is hoped that drugs targeted at mGlu receptors hold new promise to safely and effectively treat a wide range of psychiatric and neurological disorders. We hope this issue will help to spur even more interest in what we feel is an exciting future for mGlu receptor research.

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