Metabotropic Glutamate Receptor Antagonists: Novel Therapeutics for Nicotine Dependence and Depression?

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Nicotine dependence is the primary motivational factor perpetuating the tobacco smoking habit that is one of the leading preventable causes of morbidity throughout the world. This Neuroscience Perspectives article summarizes and discusses recent evidence demonstrating the critical role of glutamate transmission in nicotine dependence and emerging data suggesting that compounds acting as antagonists at metabotropic glutamate receptors may be useful therapeutics to assist people in achieving and maintaining abstinence from tobacco smoking. Metabotropic glutamate 5 receptor antagonists may be useful in decreasing the reinforcing effects of nicotine, reducing motivation for nicotine and preventing relapse during protracted abstinence, whereas metabotropic glutamate 2/3 receptor antagonists may alleviate the depression observed during the early nicotine withdrawal phase. Metabotropic glutamate 2/3 receptor antagonists may also be therapeutics for non-drug-induced depressions.

In the United States alone, tobacco smoking leads to serious illness in an estimated 8.6 million people, approximately 440,000 deaths annually, and approximately $157 billion in health-related economic costs (Centers for Disease Control and Prevention 2003). Hence, there is great need for the discovery and development of new medications to assist people in achieving and maintaining abstinence from tobacco smoking (Cryan et al 2003b). Although over 4000 chemicals in tobacco products could contribute to dependence, there is little debate that nicotine is the major component in tobacco responsible for addiction. Thus, research to promote our understanding of the neurobiology of tobacco dependence focuses on the mechanisms mediating nicotine dependence. Currently, the most widely used, albeit of limited efficacy, treatments to aid in smoking cessation are nicotine replacement therapies. Another therapy, which is non-nicotine based, is the atypical antidepressant bupropion that primarily inhibits the reuptake of dopamine. Unfortunately, first-year relapse rates with both of these treatments are as high as 80% (Jorenby et al 1999; Croghan et al 2003), further emphasizing the need for additional and alternative treatments for nicotine dependence.

Dependence on drugs of abuse, including nicotine, is often defined by (1) the persistence of drug-taking behavior despite adverse consequences; (2) the emergence of withdrawal symptoms upon abrupt cessation of drug administration; and (3) relapse to drug taking even after a period of extended abstinence after the acute withdrawal syndrome has dissipated (American Psychiatric Association 1994). Accordingly, medications targeting the reinforcing effects of acute nicotine, the alleviation of the acute withdrawal syndrome and/or prevention of relapse to drug-seeking, and drug-taking during protracted abstinence could be proven useful in smoking cessation.

Similarly to other drugs of abuse, it is hypothesized that the mesocorticolimbic dopaminergic system plays a critical role in nicotine reinforcement and dependence. Acute administration of nicotine activates excitatory nicotinic acetylcholine receptors (nAchRs) on dopamine neurons in areas such as the ventral tegmenal area (VTA). This stimulation leads to an increased firing rate of VTA dopaminergic neurons, and elevated dialysate dopamine levels in terminal dopaminergic areas, such as the shell of the nucleus accumbens (for review, Picciotto and Corrigall 2002).

Another neurotransmitter system whose function is directly modulated by nicotine administration, and which closely interacts with the mesocorticolimbic dopaminergic system, is the glutamate system. Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. The actions of glutamate are regulated by ionotropic and metabotropic glutamate (mGlu) receptors. Ionotropic glutamate receptors are primarily located postsynaptically, are glutamate-gated ion channels that when activated increase cellular excitability, and comprise the following receptor subtypes: NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate), and kainate receptors. Eight mammalian subtypes of mGlu receptors have been identified and classified into three groups (I, II, and III) based on sequence homology, signal transduction pathways, and pharmacological selectivity (for reviews, Conn and Pin 1997; Kenny and Markou 2004; Swanson et al 2005). Group I (mGlu1, mGlu5) receptors are predominately located postsynaptically where they couple to G_q-proteins to activate phospholipase C (PKC). In addition, group I receptors couple to intracellular Homer proteins that play an important role in trafficking mGlu receptors in and out of synapses and functionally connect metabotropic to ionotropic glutamate receptors. Group II (mGlu2, mGlu3) receptors are found primarily presynaptically and on glia cells, and they couple to $G_{i/o}$ proteins to negatively regulate adenylyl cyclase activity. Finally, group III (mGlu4, mGlu6, mGlu7, mGlu8) receptors are predominately presynaptic autoreceptors coupled to $G_{i/o}$ proteins to decrease adenylyl cyclase activity. Thus, mGlu receptors are slow acting and modulatory of glutamate transmission. They are also widely, but differentially, expressed in the brain. Hence, these receptors offer unique opportunities to alter in pharmacologically subtle ways glutamate transmission, and thus they affect motivated behavior and affective processes without producing gross undesirable or toxic side-effects (Conn and Pinn 1997).

Nicotine increases glutamate release by agonist actions at excitatory presynaptic nAchRs on glutamatergic terminals in various brain sites, including the VTA, nucleus accumbens, prefrontal cortex, and hippocampus (for reviews, Mansvelder and McGehee 2000; Kenny and Markou 2004). Furthermore, there are glutamatergic afferent projections, from areas such as

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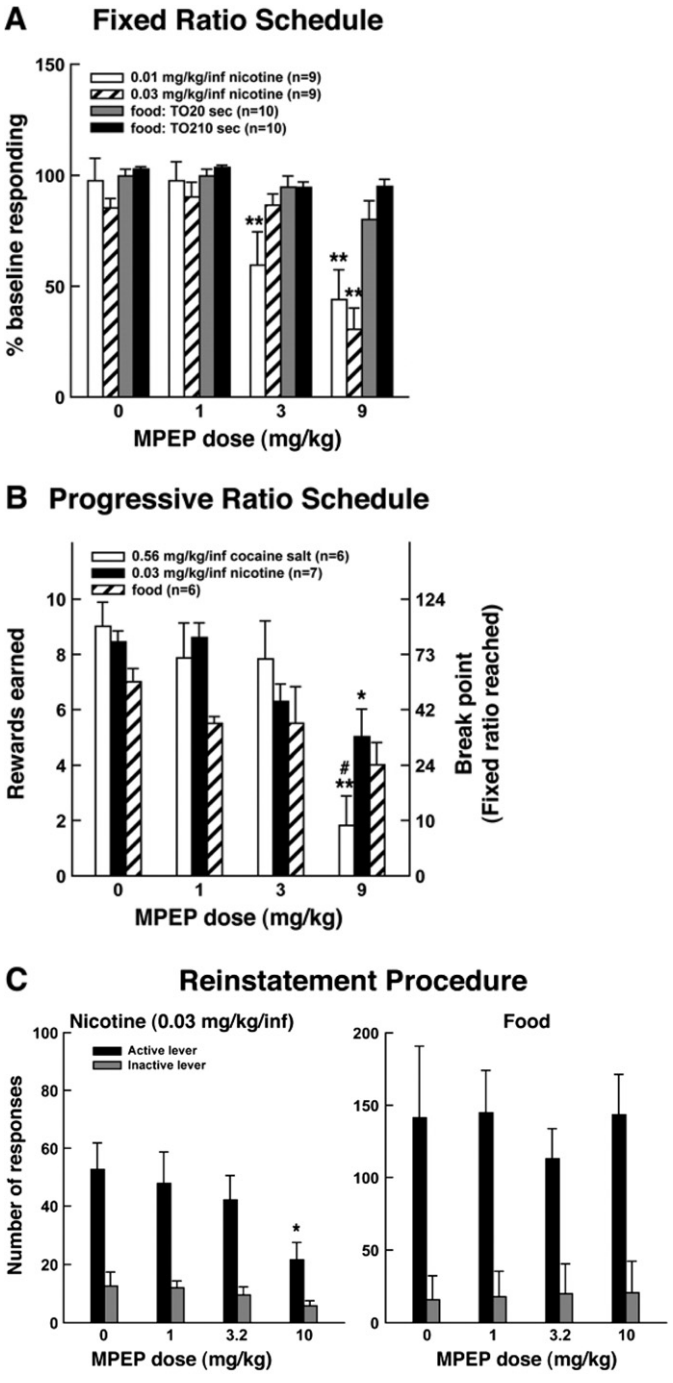

Figure 1. (A) Administration of the mGlu5 receptor antagonist MPEP decreased self-administration of either of two nicotine doses available to the rats, while not affecting responding for food on either of two schedules of food reinforcement (Fixed Ratio 5 Time Out 20 sec; Fixed Ratio 5 Time Out 210 sec), the second one of which equated reinforcement rates for nicotine and food. Data are expressed as percent of baseline responding (mean ± SEM). These results suggest that the mGlu5 receptor antagonist MPEP selectively blocked the reinforcing effects of nicotine without affecting the reinforcing effects of food or the subjects' ability to perform the task. Asterisks indicate significant differences from control conditions for each reinforcer (** $p < .01$). (Reproduced with permission from Paterson et al 2003.) **(B)** Administration of the mGlu5 receptor antagonist MPEP decreased break points for nicotine and cocaine to a greater extent than break points for food under a progressive ratio schedule of reinforcement that assesses the incentive motivation for the reinforcer. The left Y-axis indicates the number of rewards earned (mean ± SEM), and the right Y-axis indicates the corresponding number of responses (mean ± SEM) required to obtain the rewards (i.e., break point). Asterisks (* $p < .05$, ** $p < .01$) indicate significant differences from responding after vehicle treatment for the same reinforcer. Hache sign ($^{\#}$ $p < .01$) indicates a significant difference from food-maintained break points after the administration of the same dose of MPEP. Nicotine and cocaine doses were adjusted so that under baseline conditions (0 mg/kg MPEP), these doses maintained break points as similar as possible to those reached for the food reinforcer to allow direct comparisons. (Reproduced with permission from Paterson and Markou 2005). **(C)** Administration of the mGlu5 receptor antagonist MPEP decreased cue-induced reinstatement of extinguished nose-poking behavior previously maintained by intravenous nicotine (left panel), but it had no effect on responding previously maintained by food deliveries (right panel). These results indicate that MPEP decreases the ability of stimuli previously associated with nicotine administration to lead to reinitiation of nicotine-seeking behavior that was previously extinguished. Note the difference in the Y-axis scales where data are presented as number of responses for each reinforcer (mean ± SEM). $N = 12$ for each data point (except for MPEP 3.2 in the left panel where $N = 11$). Asterisks indicate significant differences from the corresponding vehicle treatment condition (* $p < .05$). (Reproduced with permission from Bespalov et al 2005).

the frontal cortex, the amygdala and the hippocampus, into brain sites that contain dopaminergic cell bodies or terminals, such as the VTA and the nucleus accumbens (for review, Kenny and Markou 2004). Thus, the nicotine-induced glutamate release acts at metabotropic and ionotropic glutamate receptors on postsynaptic dopamine neurons and increases their bursting activity and neurotransmitter release. These actions may partly mediate the reinforcing effects of acute nicotine.

Accordingly, blockade of postsynaptic mGlu5 receptors with MPEP [2-methyl-6-(phenylethynyl)-pyridine] decreased intravenous nicotine self-administration in rats and mice (Paterson et al 2003; Figure 1A), and the motivation to self-administer nicotine (Paterson and Markou 2005; Figure 1B; MPEP also decreased motivation to self-administer cocaine). These effects may be mediated by attenuation of nicotine-stimulated glutamate transmission in the mesolimbic system via blockade of postsynaptic mGlu5 receptors (Figures 3 and 4). Similar decreases in nicotine self-administration are also observed after administration of dopaminergic or nAchR antagonists (for review, Picciotto and Corrigall 2002). Furthermore, administration of MPEP decreased cue-induced reinstatement of nicotine-seeking in rats (Bespalov et al 2005; Figure 1C). It is important to emphasize that MPEP, at doses that blocked nicotine self-administration and cue-induced nicotine-seeking, had no effect on responding for food or cue-induced food-seeking behavior (Paterson et al 2003; Bespalov et al 2005). In the progressive ratio schedule, the effects of MPEP on breaking points for nicotine tended to be larger than those for food (Paterson and Markou 2005). This selectivity of the effects of MPEP for nicotine versus food reinforcement, and for nicotine-seeking versus food-seeking behavior, suggests that there are doses of MPEP that selectively affect behaviors relating to nicotine-seeking behavior without affecting motor performance, food reinforcement, or motivation for natural rewards, such as food.

The systems that develop neuroadaptations with the development of nicotine dependence and lead to the emergence of the withdrawal signs upon cessation of drug administration are likely to be the same or interacting with the systems mediating the effects of acute nicotine (Markou et al 1998). That is, drug dependence develops as an adaptation to chronic drug exposure, and thus, the withdrawal signs are often opposite in direction to the acute drug effects. Accordingly, in humans, acute nicotine administration induces a mild positive euphoric state, whereas smoking cessation leads to an aversive withdrawal syndrome characterized by affective