Discovery and Development of Novel Metabotropic Glutamine Receptor 2 (mGluR2) Agonists for Treatment of Nicotine Addiction: A Preclinical Study

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Nicotine addiction is the leading cause of preventable death worldwide. The National Institute on Drug Abuse (NIDA) reports approximately 23.6 million Americans have a nicotine use disorder. Currently available smoking cessation treatment options focus on blocking glutamate transmission, and they are mildly effective. Purpose of this investigation is to develop a metabotropic glutamate receptor (mGluR2) agonist to inhibit the reinforcing effects of nicotine and nicotine-seeking behavior. It is hypothesized that by activating metabotropic glutamine 2 receptors, which act as a negative feedback mechanism on glutamate release, will decrease the reinforcing effects of nicotine by reducing the amount of glutamate and dopamine release in the brain, thereby mitigating the pleasurable experience associated with nicotine addiction and reducing nicotine seeking behavior. Crystal structure of mGluR2 was obtained from the Protein Data Bank and the five molecules with high affinity to mGluR2 were selected using molecular docking mode. The selected molecules were screened for the reversal of nicotine addiction using nicotine-conditioned Caenorhabditis Elegans as nicotine addiction model. All the experiments were repeated in triplicate (n=3), and phosphate buffered saline was used as the negative control. Among the mGluR2 agonists tested, betacaryophyllene (BCP) and pitavastatin have shown significant nicotine de-addiction (reduced nicotine induced reflex velocity) in C. Elegans model ($p<0.05$). BCP was determined to be the best agonist. BCP demonstrated remarkable reduction of reflex velocity in nicotine-conditioned C. Elegans as compared to the control (one-way ANOVA, $p<0.05$). As BCP is not water-soluble, a nanoemulsion with globule size <200 nm was prepared.

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