Inactivation of Ornithine Aminotransferase by GABA Analogues for the Treatment of Hepatocellular Carcinoma

Published date: Dec. 5, 2017

Technology description

A potent inactivator of aminotransferases exhibiting efficacy for the treatment of addiction in an animal model and potentially other neurological and proliferative disorders. #Therapeutic #CNS #smallmolecule #biomedical #cancer #biomarker

BACKGROUND

Gamma-Aminobutyric acid (GABA) is a neurotransmitter involved in the regulation of brain neuronal activity. GABA aminotransferase (AT), an enzyme that degrades GABA resulting in the diminished levels of GABA. The low levels of GABA have been implicated in the symptoms associated with epilepsy, Parkinson's disease, Alzheimer's disease, Huntington's disease, tardive dyskinesia, and cocaine addiction. Ornithine aminotransferase (OAT), mitochondrial matrix enzyme, catalyzes the conversion of ornithine to glutamate, which can be used as substrate by glutamine synthetase to synthesize glutamine, which is critical for the growth of proliferative cells. Therefore, it was hypothesized that reducing the level of tissue glutamine concentrations by inactivation of OAT may lead to inhibition in cell proliferation and tumor growth (e.g., hepatocellular carcinoma).

ABSTRACT

Professor Richard Silverman and his colleagues at Northwestern University have designed, synthesized and evaluated conformationally-restricted, mechanism-based inhibitors of GABA-AT (for example compound 1, 2 and 3) to combat the above mentioned neurological disorders. Compound 1 is 187x more potent inactivator of GABA-AT than epilepsy drug, vigabatrin, the only FDA-approved inactivator of GABA-AT. Recently, another compound 2 showed 10x more efficient in inactivating GABA AT when compared to compound 1. To date, compound 2 is the most potent GABA-AT inactivator. The compound 2 does not inhibit the activity of hERG channel or does not inhibit or induce the seven most common CYPs (1A, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A. Plasma protein binding is only 27%, indicating a high percentage of free drug in plasma. In vivo studies in freely moving rats showed that 2 is superior to 1 in suppressing the release of dopamine in the NAcc following a cocaine or nicotine challenge (Figure on the left hand side shows the effects of an acute dose of 2 and cocaine or nicotine on 11C-raclopride uptake; upper band: control, middle band: acute cocaine or nicotine challenge and lower band: treatment with 2). Unlike Vigabatrin and 1, compound 2 also attenuated dopamine-induced increases in metabolic demand within the hippocampus, a brain region previously demonstrated to

endo spatial conditions of the environment associated with drug-induced increases in dopamine (Figure on the right hand). We also investigated these compounds for their inhibitory activity against OAT and found compounds 1, 2, and 3 inactivate OAT. Compound 3 weakly inhibits GABA-AT and is selective to OAT inhibition. Compound 2 is 9x more efficient inactivator of OAT and is a dual inhibitor of GABA-AT and OAT. All these three compounds do not inhibit aspartate-AT and alanine-AT. In vitro studies with compound 3 demonstrated a significant suppression of -fetoprotein (AFP) secretion, whereas in vivo studies demonstrated blocking the tumor growth of hepatocellular carcinoma in mice.

Application area

Therapeutic for Addiction

Advantages

Exhibits duel inhibition of GABA AT and OAT
Demonstrates proof-of-concept in animal models

Institution

Northwestern University

Inventors

Richard B. Silverman

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com