Biohacking: Anti-epileptic Drugs as Cognitive Enhancers

Antoni J. Szeglowski, Matthew J. Stroud, Namrata Madoor, Merin Panthapattu, Esteven Tineo Mateo, and Alex Ding

Advisor: James N. Jensen, Ph.D.

Introduction

Biohacking refers to the use of innovative, low-cost techniques to improve human performance. The techniques can be mechanical or chemical. Chemical biohacking includes the use of nootropics ("smart drugs"), some of which improve the response of the brain and nervous system.

The focus of this work is a family of racetams. Racetams are chemicals that contain the pyrrolidone group (Figure 1). Piracetam is a cognitive enhancer and may have anti-epileptic properties. Levetiracetam is an anti-epileptic drug which may improve certain cognitive abilities such as memory, mood, and concentration.

Background

Piracetam:

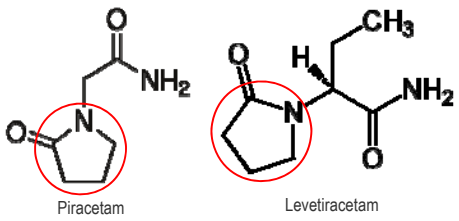
Piracetam (Figure 1) is a nootropic in the racetams group. It is a derivative of the neurotransmitter GABA. Piracetam was synthesized in 1964 by a team led by Dr. Corneliu E. Glurgea. The team of scientists quickly realized that piracetam has shown the ability to boost mental capabilities. Dr. Glurgea coined the term *nootropic*, from the Greek words meaning *mind* and *to turn*.

Piracetam is marketed outside the U.S. for neurocognitive impairments and memory loss (Malykh and Reza Sadaie, 2010). It has been used to improve cognitive function of cosmonauts. Piracetam is not authorized for sale in the United States.

Levetiracetam:

Levetiracetam (Figure 1) is an anti-epileptic drug. It has been available since 2000. The drug was originally intended to serve only as adjunctive therapy for partial-onset seizures. However, recent research has shown that levetiracetam can be used effectively in adjunct therapy for primary seizures.

Levetiracetam is used for monotherapy in the European Union (EU) although more research must be done before levetiracetam can be approved for monotherapy in the United States.



Piracetam Levetiracetam

Figure 1: Chemical Structures of Piracetam and Levetiracetam (pyrrolidone moiety is circled, source: Helmstaedter et al., 2008)

Mechanisms of Action

Piracetam

Piracetam activates α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-type glutamate receptors (Malykh and Reza Sadaie, 2010). An increased density of receptor binding sites leads to larger calcium uptake. Higher intracellular calcium uptake levels lead to increased rates of sodium dependent choline (a precursor molecule for the neurotransmitter molecule acetylcholine, needed in the autonomic nervous system) uptake in rat hippocampal synaptosomes. This is turn leads to increased neuronal impulse flow and an acceleration of cognitive functions.

Levitaracetam

Levetiracetam acts through a different pathway for its anti-epileptic activity (NIH, n.d.). Levitaracetam binds to the synaptic vesicle 2A (SV2A) protein in brain membrane and fibroblasts. This binding inhibits neuronal Ca^{2+} ion channels which in turn reduces neurotransmitter release. Subsequently, the impulse conduction across synapses is impeded which causes a decrease in excessive neuronal activity and therefore fewer seizures.

Evidence for Anti-Epileptic Activity with Piracetam

Patients with progressive myoclonus epilepsy were given daily doses of 9.6 g, 16.8 g, and 24 g piracetam over six weeks in a cross-over design (each patient receiving a placebo or two doses for two weeks each). The treatment with 24 g/day of piracetam yielded the best results. Along with a decrease of progressive myoclonus epilepsy, piracetam has also been found to improve functional disability. The dose-effect relationship was linear. Piracetam was shown to have few side effects. It did not negatively affect cognition, unlike other anti-epileptic drugs (Koskiniemi et al., 1998).

Fedi et al. (2001) studied the long-term use of piracetam with patients suffering from progressive myoclonus epilepsy. The drug was well-tolerated at doses from 3.2 to 20 g/d and improved overall scores including motor impairment, functional disability, and global assessment.

Evidence for Cognitive Enhancement Activity with Levetiracetam

Gomer et al. (2007) found that levetiracetam did not decrease the cognitive function of epilepsy patients unlike other anti-epileptic drugs. In several studies levetiracetam improved cognitive function. Improvements were seen in working memory (López-Góngora et al., 2008; Rosche et al., 2004), short-term memory (Ciesielski et al., 2006), motor functions (López-Góngora et al., 2008), psychomotor speed and concentration (Helmstaedter et al., 2008), and fluid intelligence (Rosche et al., 2004). The greatest effects of levetiracetam may seen in patients with poor cognitive function before treatment (Huang et al., 2008).

Conclusions

It appears that both piracetam and levetiracetam have both anti-epileptic and nootropic properties. Contrary to older methods of treating epilepsy, piracetam and levetiracetam do not weaken cognitive function. Rather, they improve cognitive function through improvements in working memory, short-term memory, motor functions, psychomotor speed, concentration, and fluid intelligence.

Sources

Ciesielski A.S., Samson S., and Steinhoff B.J. Neuropsychological and psychiatric impact of add-on titration of pregabalin versus levetiracetam: a comparative short-term study. *Epilepsy Behav.* 9, 424-431, 2006. As found in Eddy et al., 2011.

Eddy, C.M., Rickards, H.E. and Cavanna, A.E.. The cognitive impact of antiepileptic drugs. *Ther. Adv. Neurol. Disord.*, 4(6), 385-407, 2011.

Fedi, M., Reutens, D., Dubeau, F., Andermann, E., D'Agostino, D., and Andermann, F. Long-term efficacy and safety of piracetam in the treatment of progressive myoclonus epilepsy. *Arch Neurol.*, 58(5), 781-786, 2001.

Gomer, B., Wagner, K., Frings, L., Saar, J., Carius, A., Härle, M., Steinhoff, B.J., and Schulze-Bonhage, A. The Influence of Antiepileptic Drugs on Cognition: A Comparison of Levetiracetam with Topiramate. *Epilepsy Behav.*,10(3), 486-94, 2007.

Helmstaedter C. and Witt J.A. Cognitive outcome of antiepileptic treatment with levetiracetam versus carbamazepine monotherapy: A non-interventional surveillance trial. Epilepsy Behav 18: 74-80, 2010. As found in Eddy et al., 2011.

Huang C.-W., Pai M.-C., Tsai J.-J. Comparative cognitive effects of levetiracetam and topiramate in intractable epilepsy. *Psychiatr. Clin. Neurosci.*, 62, 548-553, 2008. As found in Eddy et al., 2011.

Koskiniemi, M., Van Vleymen, B., Hakamies, L., Lamusuo, S., and Taalas J. Piracetam Relieves Symptoms in Progressive Myoclonus Epilepsy: A Multicentre, Randomised, Double Blind, Crossover Study Comparing the Efficacy and Safety of Three Dosages of Oral Piracetam with Placebo. *J. Neurol. Neurosurg. Psychiatry,* 64(3), 344-348, 1998.

López-Góngora M., Martínez-Domeño A., García C., and Escartín A. Effect of levetiracetam on cognitive functions and quality of life: a one-year follow-up study. *Epileptic. Disord.*, 10, 297-305, 2008. As found in Eddy et al., 2011.

Malykh, A.G. and Reza Sadaie, M. Piracetam and Piracetam-Like Drugs: From Basic Science to Novel Clinical Applications to CNS Disorders. *Drugs*, 70(3), 287-312, 2010.

NIH. "LEVETIRACETAM - levetiracetam tablet." *NIH*. NIH, n.d. Web. 12 Apr. 2014. <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=fdb51f40-3ffe-46c3-8e45-02323c17b88e>.

Rosche J., Uhlmann C., Weber R., and Froscher W. Different cognitive effects of inducing levetiracetam or topiramate into an antiepileptic pharmacotherapy in patients with therapy refractory epilepsy. Neurol. *Psychiatr. Brain Res.*, 11, 109–114, 2004. As found in Eddy et al., 2011.