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Treating excitatory/inhibitory imbalance to improve learning and memory in Down Syndrome and Alzheimer's disease

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Abstract

Cognitive impairment is a dominant component of Down Syndrome (DS) and Alzheimer's Disease (AD). In addition, individuals with Down Syndrome have an extra copy of the APP gene and are at high risk for early onset of Alzheimer's Disease. A proper excitatory/inhibitory (E/I) balance is necessary for neuronal survival and for induction of the synaptic plasticity that underlies learning and memory. A disrupted E/I balance may play an important role in the learning disabilities of DS and AD. On the one hand, excessive excitatory activity at glutamatergic synapses may induce epileptic activity and excitotoxic neuronal injury. On the other hand, increased neuronal inhibition, possibly elicited as an adaptive response to over-excitation, may impact synaptic plasticity necessary for learning and memory. To test the hypothesis that the cognitive disability in DS, in AD, and in DS with AD is largely due to excessive inhibition, we have explored the therapeutic effects of antagonists of the major CNS inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and specifically antagonists of the $GABA_A$ receptor. Acute, subconvulsive doses of the non-competitive $GABA_A$ antagonist pentylenetetrazole (PTZ) given prior to a learning experience improved memory in DS model mice, but more significantly, a two week chronic regimen of daily PTZ doses 10 to 100 fold below the seizure threshold resulted in a long lasting (>2 mo) normalization of learning and memory in these DS model mice. These effects were seen in young, adult, and aged DS mice. PTZ efficacy was shown to be dependent on time of day of dosing and the occurrence of sleep.

Biography

Dr. Heller is the Lorry Lokey/Business Wire Professor of Biology and Human Biology at Stanford University. He received his PhD from Yale University in 1970 and joined the Stanford faculty in 1972 after a postdoctoral period at Scripps Institute of Oceanography. He has published over 200 papers in the areas of thermal physiology, sleep and circadian neurobiology, human performance, and recently on learning and memory in Down syndrome.

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