Cell

A New SV2A Ligand for Epilepsy

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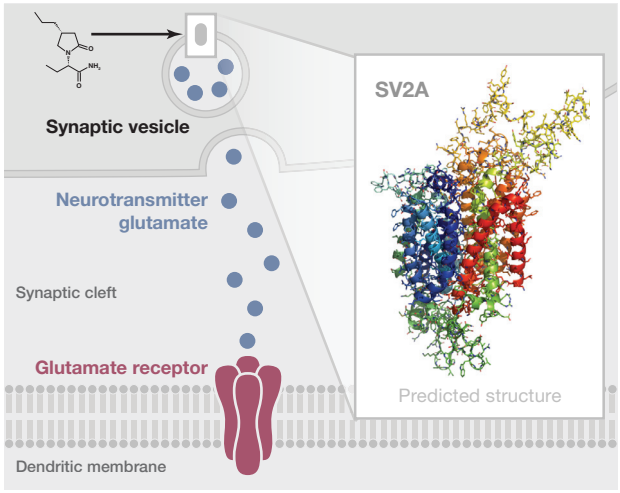
http://dx.doi.org/10.1016/j.cell.2016.09.057



Since the 1970s, racetams have been in use as cognitive enhancers. Levetiracetam was discovered to have antiseizure activity in animal models and was then found to bind to SV2A in synaptic and endocrine vesicles. Brivaracetam, an analog of levetiracetam, was identified in a medicinal chemistry campaign with the objective of discovering analogs with higher affinity at racetam-binding sites and greater antiseizure potency.

NAME
Brivaracetam {(2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide (ucb 34714); Briviact}

APPROVED FOR
Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older with epilepsy

TYPE
Small molecule

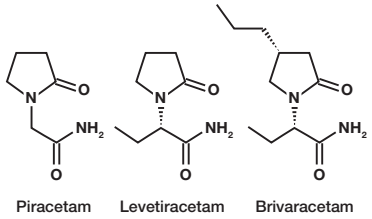
MOLECULAR TARGET
SV2A, a ubiquitous 83-kilodalton (742-amino acid) synaptic vesicle integral 12 transmembrane domain glycoprotein that is believed to function as a positive effector of synaptic vesicle exocytosis

CELLULAR TARGET
At neuronal presynaptic terminals, brivaracetam accesses the luminal side of recycling synaptic vesicles by vesicular endocytosis

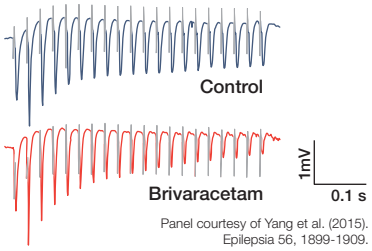
EFFECTS ON TARGET
Potent, highly selective, and reversible SV2A ligand. Binds to SV2A with 20-fold greater affinity than levetiracetam. Reduces excitatory neurotransmitter release and thus enhances synaptic depression during trains of high-frequency activity 100-fold more potently than levetiracetam. At therapeutically relevant doses, brivaracetam is expected to occupy 80% to >90% of SV2A in the brain.

DEVELOPED BY
UCB Pharma SA

Racetam analogs

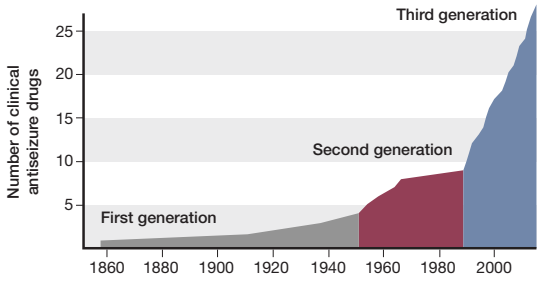


Enhances synaptic depression



Panel courtesy of Yang et al. (2015). Epilepsia 56, 1899-1909.

Antiseizure drugs



1985
Synaptic vesicle protein 2 (SV2) discovered as major component of synaptic vesicles

1992
Piracetam analog levetiracetam identified as potent antiseizure agent by screening in rodent models

1994
Saturable, stereoselective binding site for levetiracetam characterized in brain synaptic membranes

1999
Mice with targeted deletion of SV2A exhibit severe epilepsy

2002
Brivaracetam, 4′-n-propyl analog of levetiracetam, found to have potent antiseizure activity

2004
Binding site of levetiracetam identified as SV2A

2016
Brivaracetam approved in the United States and European Union for the treatment of epilepsy

1985 1990 1995 2000 2005 2010 2015 2016

References for further reading are available with this article online: www.cell.com/cell/fulltext/S0092-8674(16)31381-2