Vesicular glutamate uptake, an essential process for neuronal communication: discovery, overview, and membrane-permeable, specific inhibitors free of toxicity.

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Abstract: Glutamate is essential in the function of the central nervous system (CNS). This is achieved by properly controlled glutamate synaptic transmission, a basis for neuronal communication. Aberrant glutamate transmission is involved in many types of CNS pathophysiology. Glutamate concentration into synaptic vesicles in the nerve ending is a pivotal step in glutamate neurotransmission. Evidence now indicates that synaptic vesicles are endowed with glutamate and glycolytic ATP synthesizing enzymes as well as the vesicular glutamate transporter (VGLUT). This represents an efficient system for accumulating glutamate into synaptic vesicles. Glutamate synthesized on the surface of synaptic vesicles is immediately taken up into vesicles at the expense of ATP made on the vesicles.

Vesicular glutamate inhibition is expected to regulate glutamate transmission and potentially could alleviate some of the CNS disease symptoms associated with excessive glutamate transmission. We have recently developed membrane-permeable, VGLUT-specific inhibitors devoid of cellular toxicity, which exhibited the ability to attenuate glutamate neurotransmission. Optimization of these agents is hoped to lead to provide new insight into approaches to some of the unmet CNS drug developments.