An agonist concentration biased allosteric modulator potentiates NMDA induced ion influx in neurons

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March 30, 2022

Abstract

Background and purpose: Precisely controlled synaptic glutamate concentration is essential for normal function of the N-methyl D-aspartate (NMDA) receptors expressed in the brain. Atypical fluctuations in synaptic glutamate homeostasis lead to aberrant NMDA receptor activity that results in pathogenesis of neurological and psychiatric disorders. Therefore, glutamate concentration dependent NMDA receptor modulators will be clinically useful agents with less on-target adverse effects. Experimental approach: Two electrode voltage clamp and patch clamp electrophysiology techniques were used for pharmacological characterization. Dynamic Ca2+ and Na+ imaging were performed using cultured rat brain neurons. MTS cell viability assay was used for to study neurotoxicity. Key results: Identified a compound (coded as CNS4) that potentiates NMDA receptor currents based on the glutamate concentration. This compound increases both glycine and glutamate potency, and exhibits no voltage dependent effect. Electrophysiology recordings confirmed agonist concentration dependent changes in peak and steady state currents. Dynamic Ca2+ and Na+ imaging assays using rat brain cortical, striatal and cerebellar neurons revealed CNS4 mediated region specific disproportionate influx of Na+ compared to Ca2+ in native NMDA receptors. Direct exposure of CNS4 unaltered the viability of cultured cortical or striatal neurons, neither augmented NMDA induced neuronal death. Conclusion and implications: CNS4 is novel in chemical structure, mechanism of action and agonist concentration biased modulatory effect. This compound or its future analogs will be useful for the treatment of brain disorders associated with hypoglutamatergic neurotransmission.

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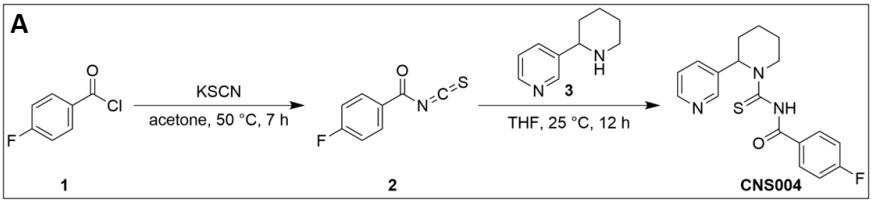

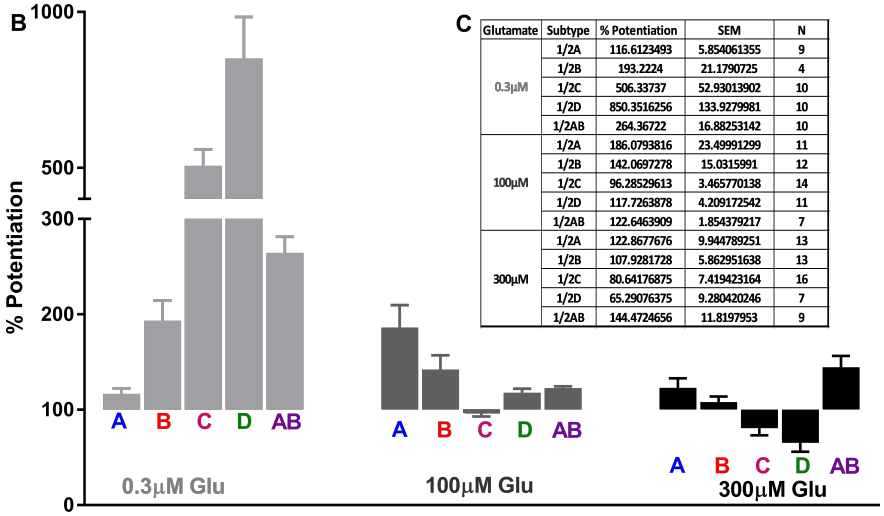

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Glutamate	Subtype	% Potentiation	SEM	N
0.3μM	1/2A	116.6123493	5.854061355	9
	1/2B	193.2224	21.1790725	4
	1/2C	506.33737	52.93013902	10
	1/2D	850.3516256	133.9279981	10
	1/2AB	264.36722	16.88253142	10
100μM	1/2A	186.0793816	23.49991299	11
	1/2B	142.0697278	15.0315991	12
	1/2C	96.28529613	3.465770138	14
	1/2D	117.7263878	4.209172542	11
	1/2AB	122.6463909	1.854379217	7
300μM	1/2A	122.8677676	9.944789251	13
	1/2B	107.9281728	5.862951638	13
	1/2C	80.64176875	7.419423164	16
	1/2D	65.29076375	9.280420246	7
	1/2AB	144.4724656	11.8197953	9