A Clickable Neurosteroid Analogue Retains NMDA Receptor Activity and Accumulates in Neurons

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NMDA receptors (NMDARs) are glutamate-gated ion channels that play important roles in the neurobiology of higher organisms. Abnormal NMDAR function is implicated in a multitude of cognitive defects, including depression, autism, schizophrenia, Alzheimer’s disease and epilepsy. Therefore, these receptors represent important therapeutic targets for many CNS disorders. Steroidlike compounds, such as pregnenolone sulfate and 24SHC, have been shown to be especially efficacious in the positive and negative modulation of NMDARs. However, the mechanisms by which these compounds are trafficked or compartmentalized in neurons are unknown. These mechanisms are highly relevant in a clinical context, as they correlate to the onset, duration, and intensity of a drug’s effect. Thus, further knowledge of compartmentalization mechanisms is needed for the synthesis of more efficacious drugs. In order to investigate the cellular trafficking of these drugs, we will develop “tagged” biological analogues. These analogues will contain: 1) a chemical handle, permitting click chemistry, and 2) a fluorescent diazirine group, facilitating high-resolution cellular imaging and colocalization of the compounds within the cell. Since these analogues are structurally similar to natural compounds, we expect they will behave comparably in their access to and actions at NMDARs. Ultimately, they will be used as probes of cellular compartmentalization, providing insight into the trafficking of natural neurosteroids at NMDARs. To assess the biological activity of these analogues, we will treat hippocampal neurons with an analogue coapplied with NMDA. For those analogues that potentiate or depress NMDA function, we will label them with a photolabeling diazirine group and analyze them with in situ photolabeling. This will inform our understanding of active and passive compartmentalization mechanisms on a cellular level. We hope that this understanding of psychoactive drug pharmacokinetics will aid in the synthesis of new drugs.