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P353. The NMDA Receptor Subunit GluN2D is a Target for Rapid Antidepressant Action

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Background: Major depressive disorder is a widespread and devastating condition that leads to enormous individual suffering and imposes a serious socioeconomic burden. Despite its vast impact, current medical treatment options are limited, and conventional antidepressants take weeks or even months to alleviate patient symptoms. Subanesthetic doses of ketamine effectively reduce depressive symptoms within hours but are often accompanied by distressing adverse effects limiting its broad clinical use. The identification of ketamine's primary target and subsequent mechanisms further downstream relevant for its antidepressant efficacy could lead to more specific interventions with fewer side effects and better treatment outcomes.

Methods: Young adult mice of both sexes were used for all experiments. Hippocampal brain slices were obtained after decapitation and patch-clamp recordings were performed according to previously published protocols to measure long-term synaptic plasticity (LTP), NMDAR currents and other cell parameters. Slices from mice expressing tdTomato in SOM-INs (SOM-Cre (SST tm2.1(cre)Zjh/J)) were used to assess SOM-INs. Protein- and RNA levels were assessed by Western Blot and RT-PCR. For behavioral assessments, the chronic despair model of depression, the Nosepoke Sucrose Preference Test in the IntelliCage and an Open Field Test were used. GRIN2D siRNA was applied by intrathecal injection together with in-vivo-jet-PEI solution.

Results: We started by investigating the behavioral antidepressant properties of ketamine in an animal chronic despair model (CDM) of depression. In CDM, animals were subjected to ten-minute forced swim sessions on five consecutive days to induce a depression-like state, followed by a rest period of two days, and different readout assessments were performed thereafter. After a single intraperitoneal injection of ketamine (10 mg/kg body weight), immobility time was significantly reduced to baseline levels and sucrose preference was normalized. In ex-

vivo hippocampal brain slices, LTP induction was completely abolished after swim stress and fully restored by ketamine treatment. In brain slices from naïve animals, ketamine facilitated LTP induction in a protocol designed to avoid ceiling effects. However, the underlying mechanism of this effect is not obvious, as hippocampal LTP is N-methyl-D-aspartate (NMDA)-dependent and ketamine is a noncompetitive NMDA receptor antagonist. The NMDAR is a heterotetramer composed of two GluN1 and two GluN2 subunits with widespread synaptic and extrasynaptic distribution on different neurons in the brain. A potential mediator of o positive modulation of LTP could be somatostatin-expressing interneurons (SOM-INs), which constitute a major subpopulation of GABAergic interneurons and provide feedback inhibition to distal dendrites of PCs in the hippocampus and the frontal cortex. As part of a feedback loop, these interneurons effectively control postsynaptic NMDA receptor activation and synaptic plasticity. In brain slices, NMDAR currents were inhibited to a larger degree in SOM-INs than in pyramidal cells. GluN2D subunits are preferentially expressed in SOM-INs, and ketamine has a higher affinity to NMDARs containing this subunit. Selective inhibition of GluN2D-containing NMDA receptors recovered stress-induced blockade of long-term synaptic potentiation, which is consolidated in later stages by structural synaptic modifications. The cellular and behavioral actions of ketamine could be fully mimicked in-vitro and in-vivo by the selective GluN2D antagonist NAB-14 and by small interfering RNA (siRNA)-mediated posttranscriptional silencing of its encoding gene GRIN2D in vivo.

Conclusions: These findings identify the GluN2D subunit of the NMDA receptor on interneurons as novel and highly specific targets for drug treatment of major depression, including RNA-based therapies.

Keywords: Depression, Synaptic Plasticity, NMDA Receptor, In-Vivo siRNA Treatment, Ketamine

Disclosure: Janssen Pharmaceuticals: Honoraria (Self), GluN2D Antagonists to Treat Depression: Patent (Self)