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**Title:** NMDA-type glutamate receptors contribute to the development of pulmonary hypertension

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**Body:** Background The NMDA receptor (NMDAR) is present in the three peripheral systems involved in Pulmonary Arterial Hypertension (PAH): immune, vascular systems and heart, but it's unknown whether it plays a role in the pathophysiology of this disease. Aims 1) Highlight the presence of NMDARs and its agonist glutamate in the pulmonary vascular wall of PAH patients. 2) Search for deregulations of this signaling pathway in PAH. 3) Test the effect of NMDAR antagonists in a rat model of PAH. Methods NMDARs and glutamate were detected by flow cytometry and confocal microscopy. Effects of two NMDAR antagonists (memantine 100mg/kg/day from day 1 to 21 and MK-801 3mg/kg/day from day 14 to 21) were studied in a rat model of monocrotaline-induced PAH. We measured hemodynamic parameters, pulmonary vascular remodeling, right heart hypertrophy, levels of circulating markers of endothelial cell (EC) dysfunction (ICAM-1 and E-selectin) by ELISA and memantine by liquid chromatography and tandem mass spectrometry. Results 1) GluN1, the obligatory subunit of NMDARs, is expressed in the walls of pulmonary arteries in PAH patients, particularly in ECs that show enhanced proliferation to glutamate. 2) In human and experimental PAH, pulmonary arterial smooth muscle cells accumulate glutamate. 3) Chronic and curative administration of memantine and MK-801 respectively, improve all parameters of PAH in the experimental model, including a reduced EC dysfunction. 4) Improvement of PAH is due to the inhibition of GluN1/GluN2A and/or GluN1/GluN2B NMDARs. Conclusion Glutamatergic signaling occurs via NMDARs in the pathophysiology of PAH and may represent an innovative therapeutic target. Support: Inserm, Paris-Sud, LabEx LERMIT, FRSR.