Schizophrenia-like endurable behavioral and neuroadaptive changes induced by ketamine administration involve Angiotensin II AT1 receptor

Occhieppo, Victoria Belén, Basmadjian, Osvaldo Martín, Marchese, Natalia Andrea, Jaime, Andrea, Pérez, Mariela Fernanda, Baiardi, Gustavo Carlos

and Bregonzio, Claudia (2022) *Schizophrenia-like endurable behavioral and neuroadaptive changes induced by ketamine administration involve Angiotensin II AT1 receptor.* Behavioural Brain Research, 425. ISSN 0166-4328

Resumen

Schizophrenia is a chronic disease affecting 1% worldwide population, of which 30% are refractory to the available treatments: thus, searching for new pharmacological targets is imperative. The acute and repeated ketamine administration are validated preclinical models that recreate the behavioral and neurochemical features of this pathology, including the parvalbumin-expressing interneurons dysfunction. Angiotensin II, through AT1 receptors (AT1-R), modulates the dopaminergic and GABAergic neurotransmission. We evaluated the AT1-R role in the long-term neuronal activation and behavioral alterations induced by repeated ketamine administration. Adult male Wistar rats received AT1-R antagonist candesartan/vehicle (days 1–10) and ketamine/saline (days 6–10). After 14 days of drug-free, neuronal activation and behavioral analysis were performed. Locomotor activity, social interaction and novel object

recognition tests were assessed at basal conditions or after ketamine challenge. Immunostaining for c-Fos, GAD67 and parvalbumin were assessed after ketamine challenge in cingulate, insular, piriform, perirhinal, and entorhinal cortices, striatum, and hippocampus. Additionally, to evaluate the AT1-R involvement in acute ketamine psychotomimetic effects, the same behavioral tests were performed after 6 days of daily-candesartan and a single-ketamine administration. We found that ketamine-induced long-lasting schizophrenia-like behavioral alterations, and regional-dependent neuronal activation changes, involving the GABAergic neurotransmission system and the parvalbumin-expressing interneurons, were AT1-R-dependent. The AT1-R were not involved in the acute ketamine psychotomimetic effects. These results add new evidence to the wide spectrum of action of ketamine and strengthen the AT1-R involvement in endurable alterations induced by psychostimulants administration, previously proposed by our group, as well as their preponderant role in the development of psychiatric pathologies.

TIPO DE DOCUMENTO: Artículo

DOI: https://doi.org/10.1016/j.bbr.2022.113809

PALABRAS CLAVE: Déficit cognitivo. Parvalbúmina. Esquizofrenia . Ketamina.

TEMAS: Q Ciencia > QD Química

R Medicina > R Medicina (General)

UNIDAD ACADÉMICA: Universidad Católica de Córdoba > Facultad de Ciencias Químicas