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ANTIDEPRESSANT ACTIONS OF KETAMINE ENGAGE CELLULAR MECHANISMS OF ENDOPLASMIC RETICULUM STRESS BY THE EIF2α PATHWAY

POSTER SESSION 04 - SECTION: RISK FACTORS AND TREATMENT OF MOOD DISORDERS

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Aims: Depression is a devastating mood disorder that causes profound disability worldwide. Despite the growing number of antidepressant medications available, treatment options for depression are limited. Therefore, it is imperative to understand the etiology and pathophysiology of depression to discover novel therapeutic targets of action. Here, we explore how endoplasmic reticulum (ER) stress might play an important role in the pathophysiology of depression and how the antidepressant ketamine actions involve ER pathways
Methods: We generated a mouse model of ER stress in serotonin (5-HT) neurons using the stressor tunicamycin (200 µg/µl). We examined ER/UPR pathway markers by Western blot, neuroplasticity gene expression (BDNF, TrkB, VEGF, Neuritin, PSD95, and Zif268) by in situ hybridization, 5-HT release by microdialysis, and behavioral depressive-like phenotype. Ketamine (10 mg/kg, i.p.) was used to reverse the ER stress-induced depressive mouse model.
Results: Tunicamycin-induced ER stress in 5-HT neurons left a time-dependent increase in GRP78 and CHOP protein levels. In addition, increased phosphorylation of eIF2α and eEF2 was found, suggesting activation of PERK pathway. Tunicamycin-treated mice exhibited an anxious/depressive phenotype, reduced 5-HT release in the medial prefrontal cortex, and changes in neuroplasticity gene expression in 5-HT projection areas. A single dose of ketamine reversed the depressive phenotype 30 minutes later, which is associated with reduced levels of phosphorylated eIF2α and recovery of BDNF expression.
Conclusions: The results strongly indicate that ER stress and UPR may represent cellular pathogenic mechanisms in the development of mood disorders and that eIF2α pathway is central for the antidepressant activity of ketamine.

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35163729: Pavia-Collado R, Rodríguez-Aller R, Alarcón-Arís D, Miquel-Rio L, Ruiz-Bronchal E, Paz V, Campa L, Galofré M, Sgambato V, Bortolozzi A
Up and Down γ-Synuclein Transcription in Dopamine Neurons Translates into Changes in Dopamine Neurotransmission and Behavioral Performance in Mice.
The synuclein family consists of α-, β-, and γ-Synuclein (α-Syn, β-Syn, and γ-Syn) expressed in the neurons and concentrated in synaptic terminals. While α-Syn is at the center of interest due to its implication in the pathogenesis of Parkinson's disease (PD) and other synucleinopathies, limited information exists on the other members. The current study aimed at investigating the biological role of γ-Syn controlling the midbrain dopamine (DA) function. We generated two different mouse models with: (i) γ-Syn overexpression induced by an adeno-associated viral vector and (ii) γ-Syn knockdown induced by a ligand-conjugated antisense oligonucleotide, in order to modify the endogenous γ-Syn transcription levels in midbrain DA neurons. The progressive overexpression of γ-Syn decreased DA neurotransmission in the nigrostriatal and mesocortical pathways. In parallel, mice evoked motor deficits in the rotarod and impaired cognitive performance as assessed by novel object recognition, passive avoidance, and Morris water maze tests. Conversely, acute γ-Syn knockdown selectively in DA neurons facilitated forebrain DA neurotransmission. Importantly, modifications in γ-Syn expression did not induce the loss of DA neurons or changes in α-Syn expression. Collectively, our data strongly suggest that DA release/re-uptake processes in the nigrostriatal and mesocortical pathways are partially dependent on substantia nigra pars compacta /ventral tegmental area (SNc/VTA) γ-Syn transcription levels, and are linked to modulation of DA transporter function, similar to α-Syn.
Int J Mol Sci, 2022; 23
35022720: Castañé A, Cano M, Ruiz-Avila L, Miquel-Rio L, Celada P, Artigas F, Riga MS
Dual 5-HT3 and 5-HT6 Receptor Antagonist FPPQ Normalizes Phencyclidine-Induced Disruption of Brain Oscillatory Activity

in Rats.
Schizophrenia is a severe mental disorder featuring psychotic, depressive, and cognitive alterations. Current antipsychotic drugs preferentially target dopamine D2-R and/or serotonergic 5-HT2A/1A-R. They partly alleviate psychotic symptoms but fail to treat negative symptoms and cognitive deficits. Here we report on the putative antipsychotic activity of (1-[(3-fluorophenyl)sulfonyl]-4-(piperazin-1-yl)-1H-pyrrolo[3,2-c]quinoline dihydrochloride) (FPPQ), a dual serotonin 5-HT3-R/5-HT6-R antagonist endowed with pro-cognitive properties. FPPQ fully reversed phencyclidine-induced decrease of low-frequency oscillations in the medial prefrontal cortex of anaesthetized rats, a fingerprint of antipsychotic activity. This effect was mimicked by the combined administration of the 5-HT3-R and 5-HT6-R antagonists ondansetron and SB-399 885, respectively, but not by either drug alone. In freely moving rats, FPPQ countered phencyclidine-induced hyperlocomotion and augmentation of gamma and high-frequency oscillations in medial prefrontal cortex, dorsal hippocampus, and nucleus accumbens. Overall, this supports that simultaneous blockade of 5-HT3R and 5-HT6-R-like that induced by FPPQ-can be a new target in antipsychotic drug development.
Int J Neuropsychopharmacol, 2022; 25
34852293: Alarcón-Arís D, Pavia-Collado R, Miquel-Rio L, Coppola-Segovia V, Ferrés-Coy A, Ruiz-Bronchal E, Galofré M, Paz V, Campa L, Revilla R, Montefeltro A, Kordower JH, Vila M, Artigas F, Bortolozzi A
Corrigendum to "Anti-α-synuclein ASO delivered to monoamine neurons prevents α-synuclein accumulation in a Parkinson's disease-like mouse model and in monkeys" [EBioMedicine 2020; 59:102944].
EBioMedicine, 2021; 74
33805843: Pavia-Collado R, Cóppola-Segovia V, Miquel-Rio L, Alarcón-Aris D, Rodríguez-Aller R, Torres-López M, Paz V, Ruiz-Bronchal E, Campa L, Artigas F, Montefeltro A, Revilla R, Bortolozzi A
Intracerebral Administration of a Ligand-ASO Conjugate Selectively Reduces α-Synuclein Accumulation in Monoamine Neurons of Double Mutant Human A30P*A53T*α-Synuclein Transgenic Mice.
α-Synuclein (α-Syn) protein is involved in the pathogenesis of Parkinson's disease (PD). Point mutations and multiplications of the α-Syn, which encodes the gene, are correlated with early-onset PD, therefore the reduction in a-Syn synthesis could be a potential therapy for PD if delivered to the key affected neurons. Several experimental strategies for PD have been developed in recent years using oligonucleotide therapeutics. However, some of them have failed or even caused neuronal toxicity. One limiting step in the success of oligonucleotide-based therapeutics is their delivery to the brain compartment, and once there, to selected neuronal populations. Previously, we developed an indatraline-conjugated antisense oligonucleotide (IND-1233-ASO), that selectively reduces α-Syn synthesis in midbrain monoamine neurons of mice, and nonhuman primates. Here, we extended these observations using a transgenic male mouse strain carrying both A30P and A53T mutant human α-Syn (A30P*A53T*α-Syn). We found that A30P*A53T*α-Syn mice at 4-5 months of age showed 3.5-fold increases in human α-Syn expression in dopamine (DA) and norepinephrine (NE) neurons of the substantia nigra pars compacta (SNc) and locus coeruleus (LC), respectively, compared with mouse α-Syn levels. In parallel, transgenic mice exhibited altered nigrostriatal DA neurotransmission, motor alterations, and an anxiety-like phenotype. Intracerebroventricular IND-1233-ASO administration (100 µg/day, 28 days) prevented the α-Syn synthesis and accumulation in the SNc and LC, and recovered DA neurotransmission, although it did not reverse the behavioral phenotype. Therefore, the present therapeutic strategy based on a conjugated ASO could be used for the selective inhibition of α-Syn expression in PD-vulnerable monoamine neurons, showing the benefit of the optimization of ASO molecules as a disease modifying therapy for PD and related α-synucleinopathies.
Int J Mol Sci, 2021; 22
33303736: Tarrés-Gatius M, Miquel-Rio L, Campa L, Artigas F, Castañé A
Involvement of NMDA receptors containing the GluN2C subunit in the psychotomimetic and antidepressant-like effects of ketamine.
Acute ketamine administration evokes rapid and sustained antidepressant effects in treatment-resistant patients. However, ketamine also produces transient perceptual disturbances similarly to those evoked by other non-competitive NMDA-R antagonists like phencyclidine (PCP). Although the brain networks involved in both ketamine actions are not fully understood, PCP and ketamine activate thalamo-cortical networks after NMDA-R blockade in GABAergic neurons of the reticular thalamic nucleus (RtN). Given the involvement of thalamo-cortical networks in processing sensory information, these networks may underlie psychotomimetic action. Since the GluN2C subunit is densely expressed in the thalamus, including the RtN, we examined the dependence of psychotomimetic and antidepressant-like actions of ketamine on the presence of GluN2C subunits, using wild-type and GluN2C knockout (GluN2CKO) mice. Likewise, since few studies have investigated ketamine's effects in females, we used mice of both sexes. GluN2C deletion dramatically reduced stereotyped (circling) behavior induced by ketamine in male and female mice, while the antidepressant-like effect was fully preserved in both genotypes and sexes. Despite ketamine appeared to induce similar effects in both sexes, some neurobiological differences were observed between male and female mice regarding c-fos expression in thalamic nuclei and cerebellum, and glutamate surge in prefrontal cortex.

In conclusion, the GluN2C subunit may discriminate between antidepressant-like and psychotomimetic actions of ketamine. Further, the abundant presence of GluN2C subunits in the cerebellum and the improved motor coordination of GluN2CKO mice after ketamine treatment suggest the involvement of cerebellar NMDA-Rs in some behavioral actions of ketamine.
Transl Psychiatry, 2020; 10

32810825: Alarcón-Arís D, Pavia-Collado R, Miquel-Rio L, Coppola-Segovia V, Ferrés-Coy A, Ruiz-Bronchal E, Galofré M, Paz V, Campa L, Revilla R, Montefeltro A, Kordower JH, Vila M, Artigas F, Bortolozzi A

Anti-α-synuclein ASO delivered to monoamine neurons prevents α-synuclein accumulation in a Parkinson's disease-like mouse model and in monkeys.

Progressive neuronal death in monoaminergic nuclei and widespread accumulation of α-synuclein are neuropathological hallmarks of Parkinson's disease (PD). Given that α-synuclein may be an early mediator of the pathological cascade that ultimately leads to neurodegeneration, decreased α-synuclein synthesis will abate neurotoxicity if delivered to the key affected neurons.
EBioMedicine, 2020; 59