Preclinical Evaluation of Ropanicant, a Nicotinic Acetylcholine α4β2 Receptor Antagonist in Animal Models of Depression

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Introduction

Depression is a common, chronic, disabling and life-threatening mental disorder. It involves a depressed mood or loss of pleasure or interest in activities for long periods of time. Globally, an estimated 3.8% of the population experience depression, including 5% of adults. Approximately 280 million people in the world have depression. This pervasive condition can lead to suicide. More than 700, 000 people die due to suicide every year, a staggering statistic that underscores its widespread impact. Delving into the intricate mechanisms underlying depression, the cholinergic theory offers insights into the delicate balance between the adrenergic and cholinergic systems in individuals grappling with this mood disorder. It suggests that an imbalance within these neural pathways may contribute to the manifestation of depressive symptoms. Ropanicant, an α4β2 receptor antagonist, is considered a promising candidate in the quest for effective treatments. This novel compound targets the nicotinic acetylcholine α4β2 receptors, presenting a potential avenue for therapeutic intervention. Its efficacy was evaluated in animal models of depression, anhedonia and cognition.

Methods and Results

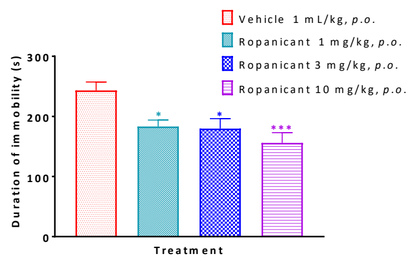
In-vivo Pharmacokinetics and Brain Penetration Profile in Wistar Rats

Parameters	3 mg/kg, *p.o.*	1 mg/kg, *i.v.*
C_{max} (ng/mL)	840 ± 301	-
T_{max} (hr)	0.25	-
AUC_{0-24h} (ng*hr/mL)	1553 ± 198	582 ± 30
$T_{1/2}$ (h)	1.4 ± 0.2	1.00 ± 0.16
MRT Last (hr)	1.8 ± 0.2	1.03 ± 0.03
CL (mL/min/kg)	-	28.5 ± 1.6
Vd_{ss} (L/kg)	-	2.5 ± 0.5
Bioavailability (%)		**89 ± 11**

Time (hr)	Brain (ng/g)	Plasma (ng/mL)	C_{brain}/C_{plasma}
1 mg/kg,*p.o.*			
0.5	217 ± 179	140 ± 97	1.4 ± 0.3
1	92 ± 31	50 ± 14	1.8 ± 0.2
2	44 ± 25	27 ± 15	1.6 ± 0.6
3 mg/kg,*p.o.*			
0.5	932 ± 569	385 ± 184	2.3 ± 0.4
1	516 ± 112	193 ± 33	2.7 ± 0.3
2	219 ± 35	93 ± 25	2.4 ± 0.3

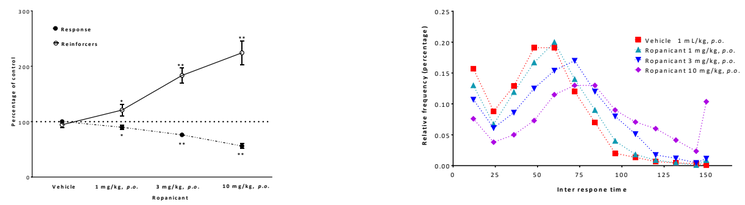
Data represents Mean ± SD.

Forced Swim Test in Wistar Rats



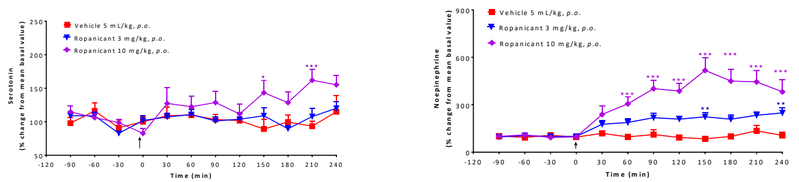
Data represents Mean ± SEM. *p<0.05, ***p<0.001, (Dunnett's multiple comparisons test).

Differential Reinforcement of Low-Rate 72 Seconds in Sprague Dawley Rats



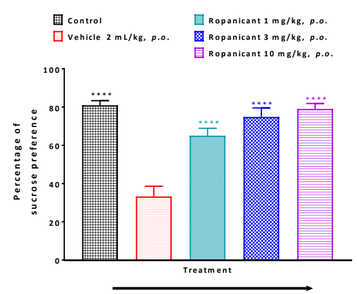
Data represents Mean ± SEM. *p<0.05, **p<0.01 (Dunnett's multiple comparisons test)

Norepinephrine and Serotonin Modulation in Prefrontal Cortex of Male Wistar Rats



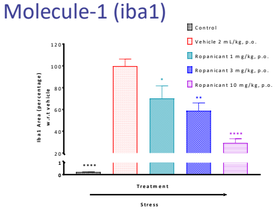
Data represents Mean ± SEM. *p<0.05, **p<0.01, ***p<0.001 (Dunnett's multiple comparisons test).

Chronic Mild Stress in Wistar Rats: Sucrose Preference Test

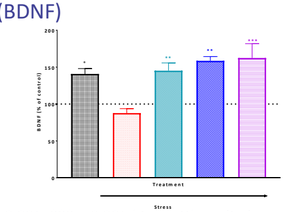


Data represents Mean ± SEM. ****p<0.0001 (Dunnett's multiple comparisons test).

Ionized Calcium Binding Adaptor Molecule-1 (iba1)



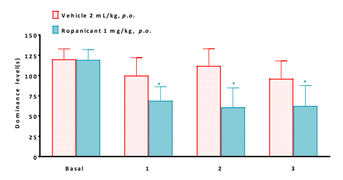
Brain derived neurotrophic factor (BDNF)



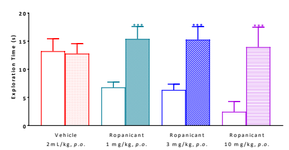
Data represents Mean ± SEM. *p<0.05, **p<0.01, ***p<0.001, ***p<0.001 (Dunnett's multiple comparisons test).

Differentiation Profile in Rat Models

Dominant Submissive Assay (Faster onset)

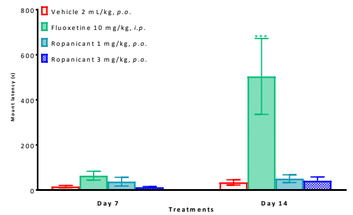


Object Recognition Task (Procognitive)



Data represents Mean ± SEM. *p<0.05, ***p<0.001, (Dunnett's multiple comparisons test or t-test).

Sexual Dysfunction Assay (No Sexual Dysfunction)



Data represents Mean ± SEM. ***p<0.001 (Dunnett's multiple comparisons test).

Conclusions

- Ropanicant, in the forced swim test, exhibited a tangible reduction in the duration of immobility-a hallmark feature of depressive behavior.
- Ropanicant demonstrated increase in serotonin and norepinephrine levels in cortex which may explain the antidepressant property.
- Ropanicant reversed anhedonia in chronic mild stress conditions.
- Ropanicant reduced the iba1 levels and increased BDNF levels in rats which could be the possible mechanism of action in conditions of chronic mild stress.
- Ropanicant was found to be devoid of sexual side effects, common with conventional antidepressants. Ropanicant has procognitive properties.
- Promising preclinical findings beckons further exploration into the therapeutic potential of Ropanicant, offering a glimmer of hope for those navigating the labyrinth of depression. Phase 2 study evaluating the safety and efficacy of Ropanicant in patients with moderate to severe MDD will inform the clinical utility (NCT06126497).