Efficacy and Safety of SUVN-N9503012, A Selective 5-HT1A Partial Agonist For the Symptomatic Treatment of Neurodegenerative Disorders

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Introduction:

Behavioral and psychological symptoms of dementia involve disturbed perception, mood disturbances, behavior changes, and thought content, leading to institutional care. While antipsychotics are prescribed, long-term use of these drugs is associated with an increased risk of mortality and an increased frequency of cerebrovascular events. The hippocampus, which plays a central role in cognition, is characterized by a high concentration of serotonin (5-hydroxytryptamine; 5-HT) 1A receptor binding sites. The 5-HT1A receptors have been implicated in various neuropsychiatric illnesses such as depression and anxiety. In the current research, we describe the profile of one of our lead compounds. SUVN-N9503012 is a potent and selective 5-HT1A receptor partial agonist being developed for the potential treatment of neurodegenerative diseases.

Methods and Results:

In-vitro Profile:

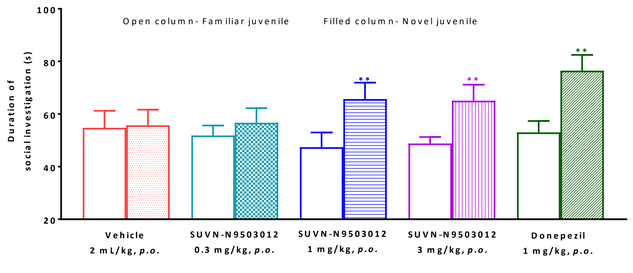
Assay	Results
5-HT1A Binding hKi	1.5 nM
5-HT1A Functional-GTPγ hEC_{50}	11.7 nM
5-HT1A Functional-cAMP hEC_{50}/E_{max}	36 nM /52%
Nature of Binding	Partial agonist
Selectivity towards other receptors, D2S, 5-HT2A, H1, Adα1b and SERT	>350-fold selectivity

In-vivo Pharmacokinetics:

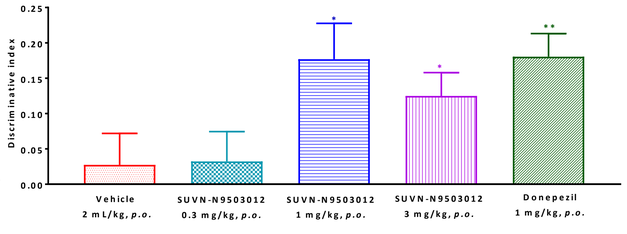
Parameters	Rat (Wistar)	Dog (Beagle)
Dose (mg/kg)	3	1.5
C_{max} (ng/mL)	110 ± 41	146 ± 33
T_{max} (h)	0.67	1
AUC_{0-t} (ng·h/mL)	578 ± 262	1208 ± 1013
$T_{1/2}$ (h)	4.9 ± 2.4	4.5 ± 3.2
F (%)	42 ± 19	51 ± 19
C_{brain}/C_{plasma}	6.9 ± 0.6	-

Mean ± SD; F: Bioavailability

Social Recognition Task in Rats - Reverses Episodic Memory Deficits:

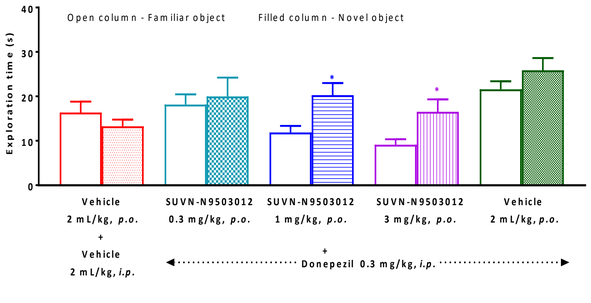


Results are Mean ± SEM, **p<0.01 Vs. familiar juvenile.

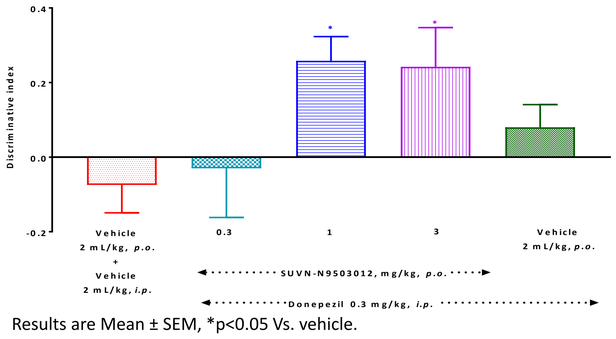


Results are Mean ± SEM, *p<0.05,**p<0.01 Vs. vehicle.

Object Recognition Task in Rats - Potentiates The Pro-cognitive Effects of Donepezil:

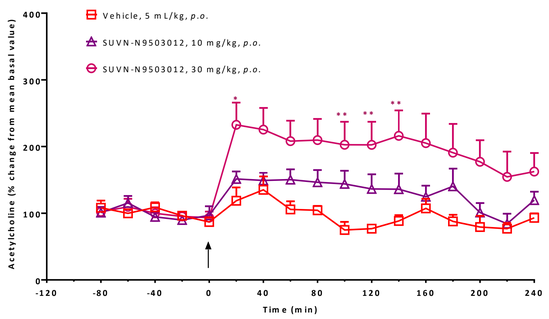


Results are Mean ± SEM,*p<0.05 Vs. familiar object.

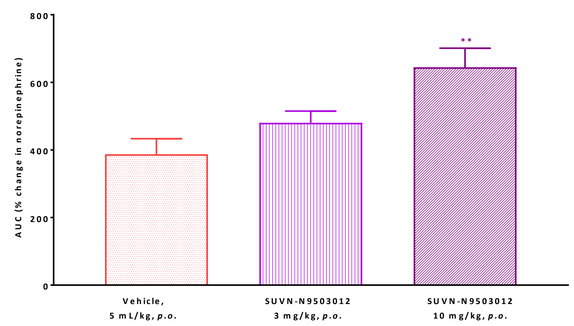


Results are Mean ± SEM, *p<0.05 Vs. vehicle.

Acetylcholine Modulation in Rat Cortex:

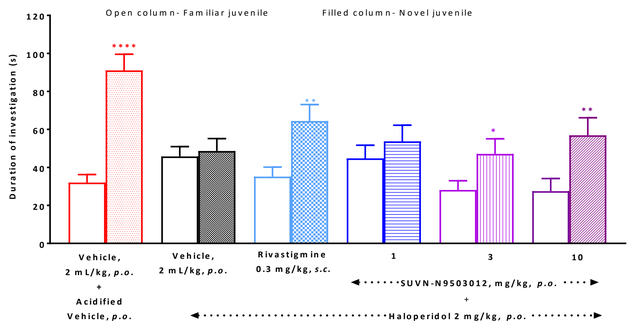


Norepinephrine Modulation in Rat Cortex:

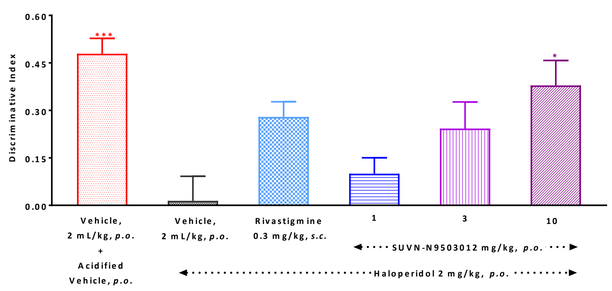


Results are Mean ± SEM, *p<0.05,**p<0.01 Vs. vehicle.

Social Olfactory Memory Task - Reverses Parkinsons like Dementia in Rats:

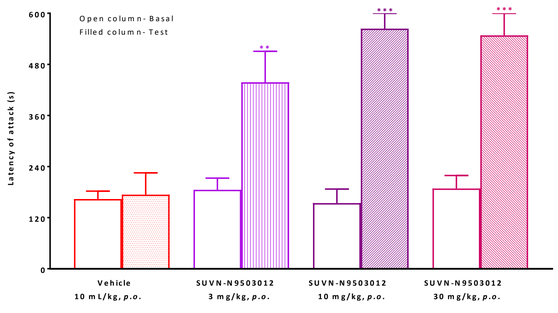


Results are Mean ± SEM, *p<0.05, **p<0.01, Vs. familiar juvenile.

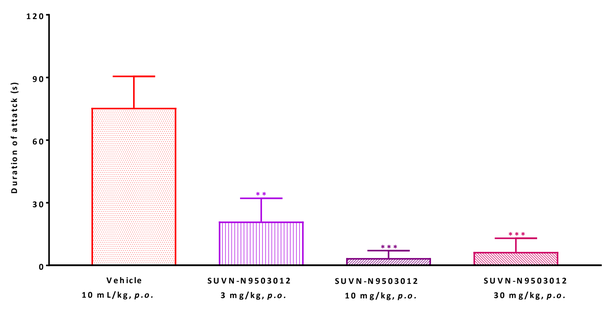


Results are Mean ± SEM, *p<0.05,***p<0.001 Vs. haloperidol.

Resident Intruder Task - Reverses Aggressive Behaviors in Mice:



Results are Mean ± SEM, **p<0.01 ***p<0.01, Vs. familiar juvenile.



Results are Mean ± SEM, **p<0.01,***p<0.001 Vs. vehicle.

Conclusions:

- SUVN-N9503012 is a novel, potent, selective 5-HT1A receptor partial agonist.
- Showed good pharmacokinetic profile in rats and dogs.
- Showed excellent brain penetration in rats.
- Showed pro-cognitive effects in diverse animal models.
- Potentiated the efficacy of Donepezil.
- Modulated acetylcholine and norepinephrine levels in rat frontal cortex.
- A dose dependent efficacy in mice resident intruder task signifies its potential to reduce agitation.
- These results support the development of SUVN-N9503012 for the potential treatment of neurodegenerative diseases.