

Mechanism of Action, Preclinical Efficacy, and Safety Evaluation of SAN711/ACP-711, a Novel GABA_A Subunit α_3 Selective Modulator

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Disclosures

Affiliation / Financial interest	Commercial company
Stock shareholder:	Acadia Pharmaceuticals Inc.
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ACP-711 – Potential Treatment for Essential Tremor

- **Essential tremor**

- Treatments including GABAergic medications, β -blockers, antiseizure medications, and benzodiazepines can have significant **adverse events**^{1,2}

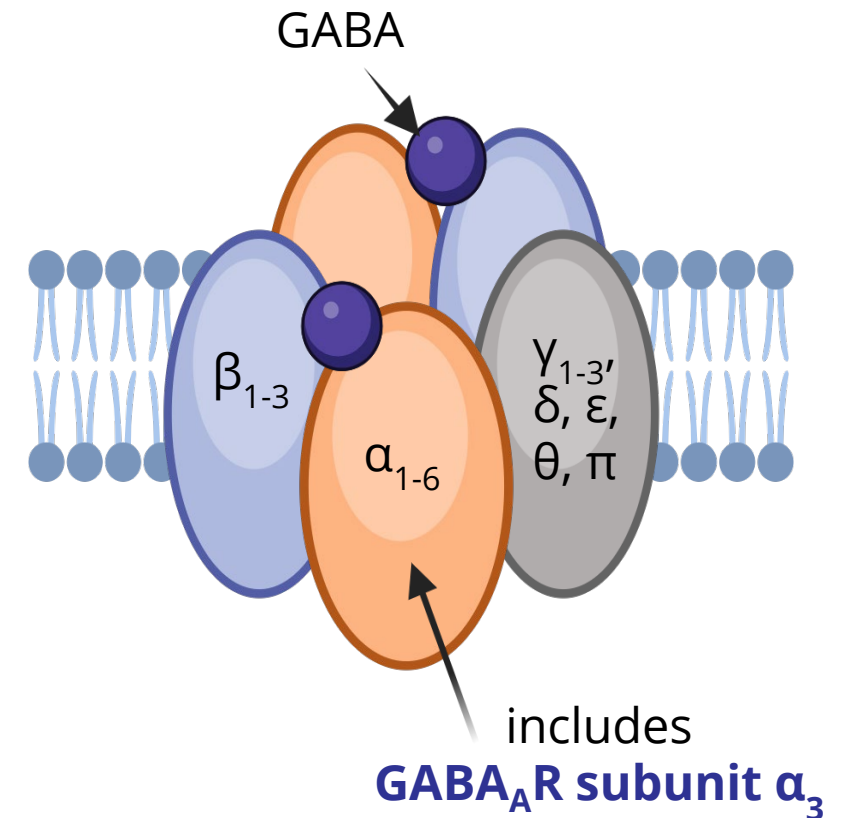
- **ACP-711 (SAN711)**

- Novel **GABA_AR subunit α_3** -selective modulator
- Designed to have an **improved safety profile** vs other GABAergic drugs

- **Objective: Evaluate nonclinical profile of ACP-711 pharmacology, effectiveness, and safety**

- **In vitro**
- **Animal model of essential tremor**

GABA type A Receptor (GABA_AR)



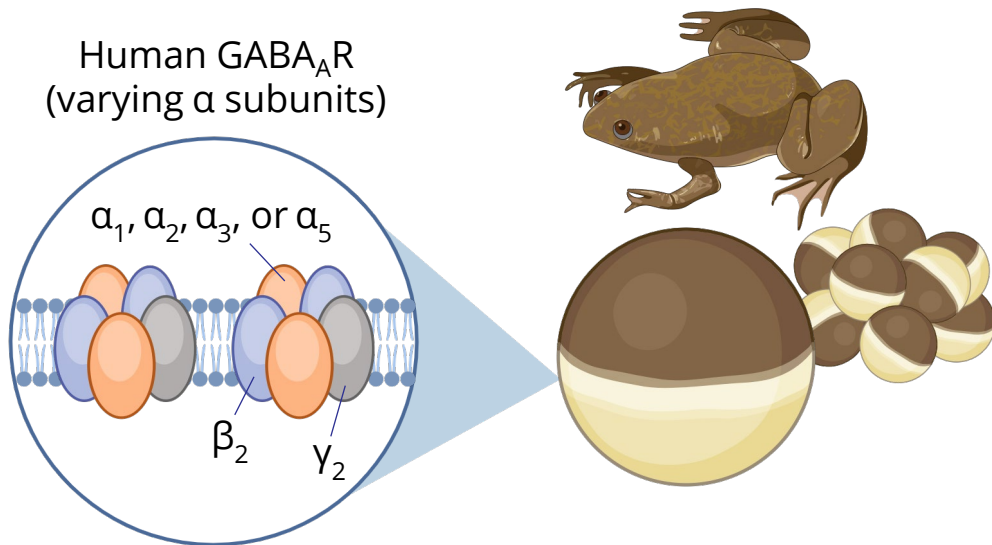
Schematic created in BioRender. Ayala, J. (2025) <https://BioRender.com/v99zntu>.

GABA, γ -aminobutyric acid; GABA_AR, GABA type A receptor.

References: 1. Bruno E, et al. *Cochrane Database Syst Rev*. 2016;10(10):CD009682. 2. Pal PK. *Ann Indian Acad Neurol*. 2011;14(suppl 1):S25-S28.

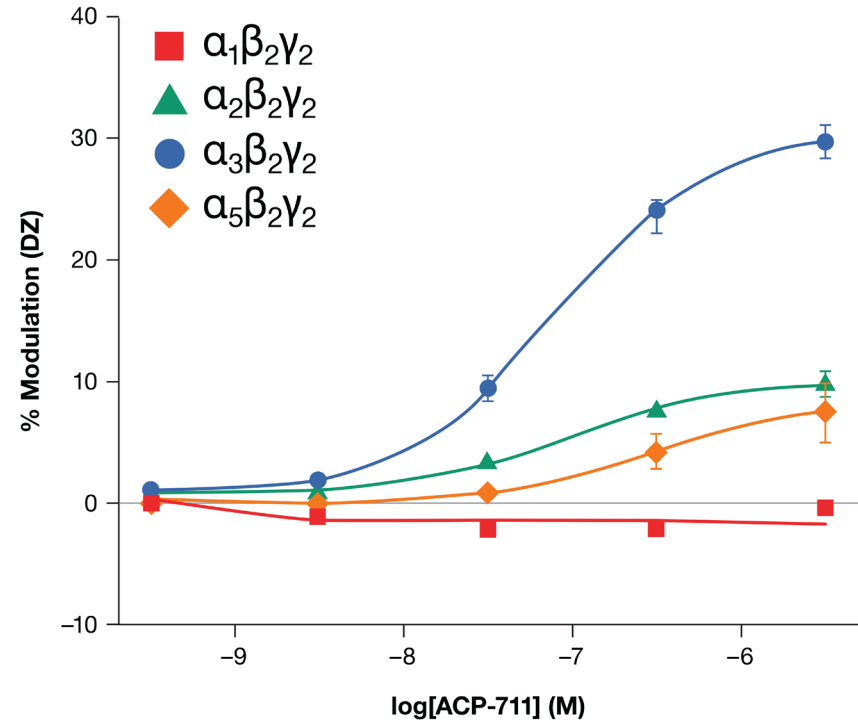
ACP-711 – A Potent PAM of GABA_A Receptor Subunit α_3

Xenopus oocyte model



- Efficiency selectivity order:

$$\alpha_3\beta_2\gamma_2 > \alpha_2\beta_2\gamma_2 = \alpha_5\beta_2\gamma_2 \gg \alpha_1\beta_2\gamma_2$$



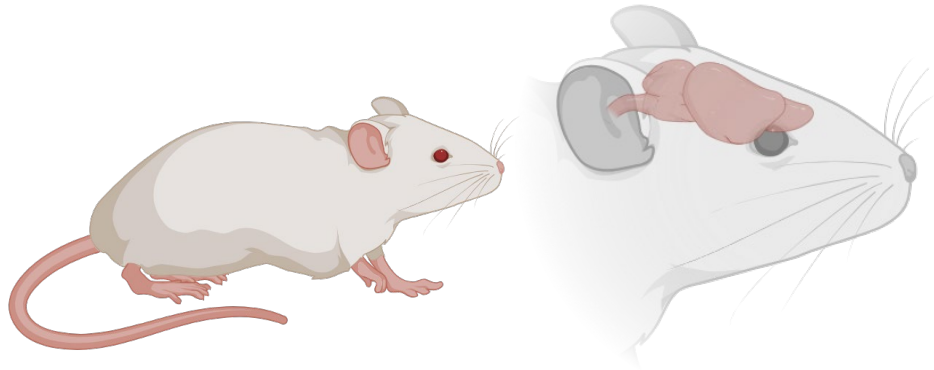
	$\alpha_1\beta_2\gamma_2$	$\alpha_2\beta_2\gamma_2$	$\alpha_3\beta_2\gamma_2$	$\alpha_5\beta_2\gamma_2$
$E_{max}(\%)$	-1.4	10	31	8.5
$EC_{50}(nM)$	Undetermined	90	85	280
Number of oocytes	8	3	14	6

Values shown in the graph are means $\pm$ SE. Schematic created in BioRender. Ayala, J. (2025) <https://BioRender.com/v99zntu>.

DZ, diazepam; EC_{50} , half-maximal effective concentration; E_{max} , maximum efficacy; GABA_AR, γ -aminobutyric acid type A receptor; PAM, positive allosteric modulator.

ACP-711 – Adequate, Dose-Dependent Brain GABA_A Receptor Occupancy

Mouse forebrain GABA_A receptor binding
(% ³H-flumazenil displacement)
2 h after oral ACP-711



- **Based on percentage inhibition of binding**
 - **Estimated ED₅₀: 0.7 mg/kg**
 - **Plasma concentration: 0.32 µM**

Oral dose (mg/kg)	Inhibition of binding (%) ^a	Plasma concentration (µM) ^b
0.01	13	0.035
1	57	0.5
10	97	8.0

Schematic created in BioRender. Ayala, J. (2025) <https://BioRender.com/v99zntu>.

EC₅₀, half-maximal effective concentration; GABA_AR, γ-aminobutyric acid type A receptor; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

^aPercentage inhibition after 2 h oral administration of ACP-711 followed by tail vein injection of 2.0 µCi of ³H-flumazenil 10 min before sacrifice and analysis of mouse forebrain tissue.

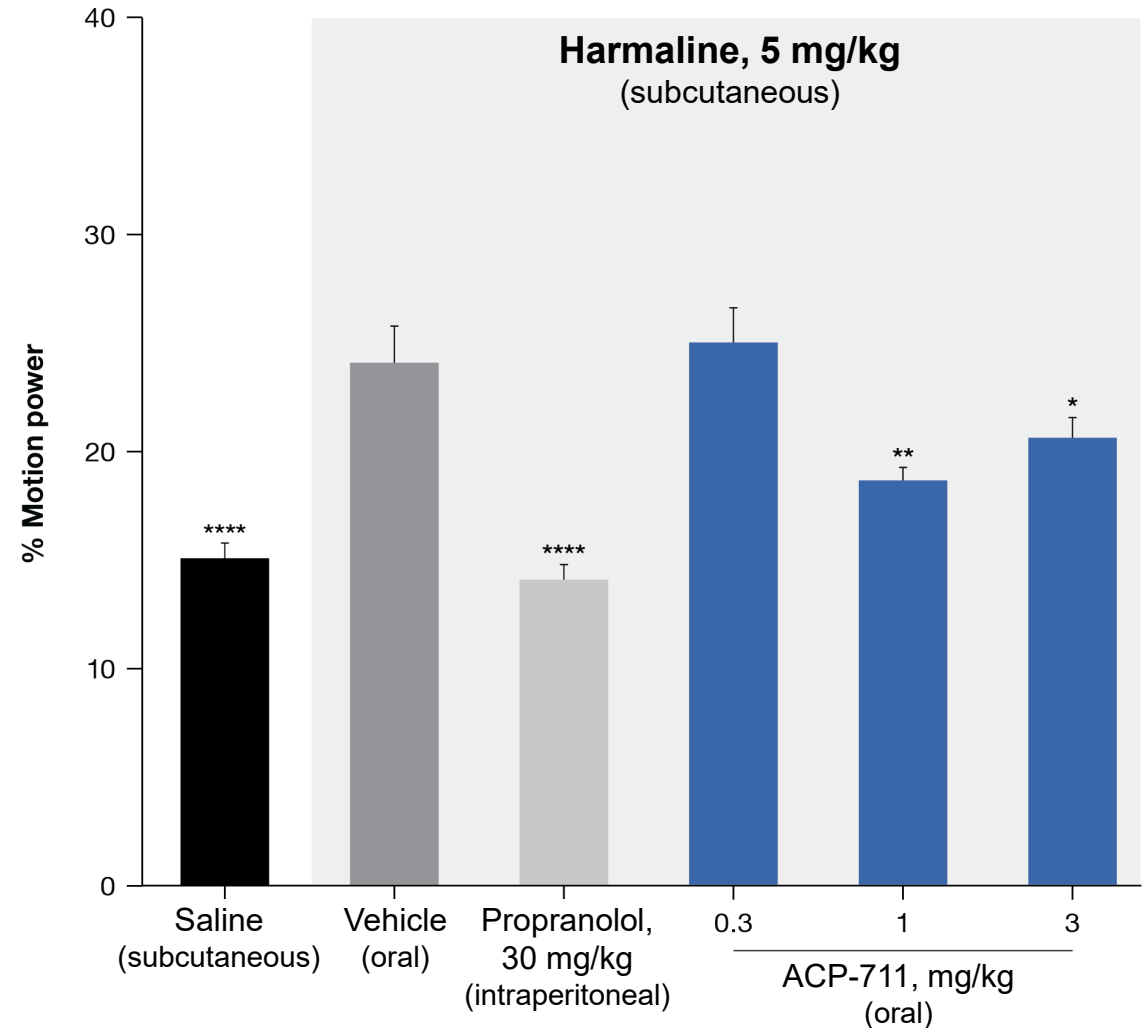
^bDetermined using LC-MS/MS of plasma samples.

ACP-711 – Reduction of Harmaline-Induced Tremors in Rats

Harmaline rat model



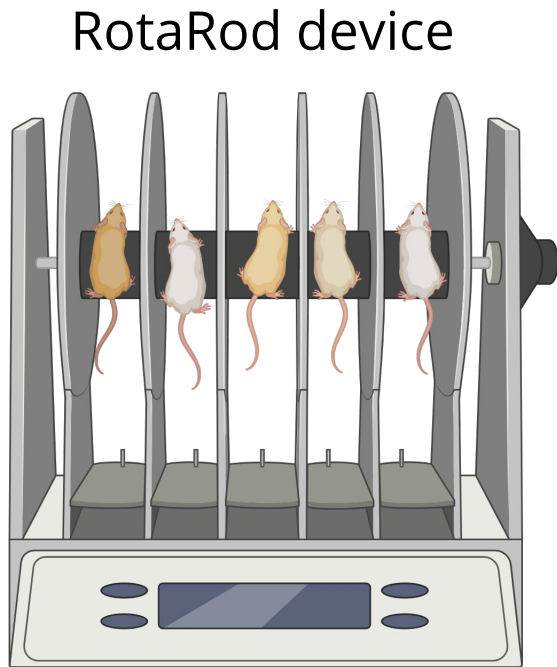
- **ACP-711 minimal effective dose: 1 mg/kg**
- **Propranolol (positive control) animals were recumbent**



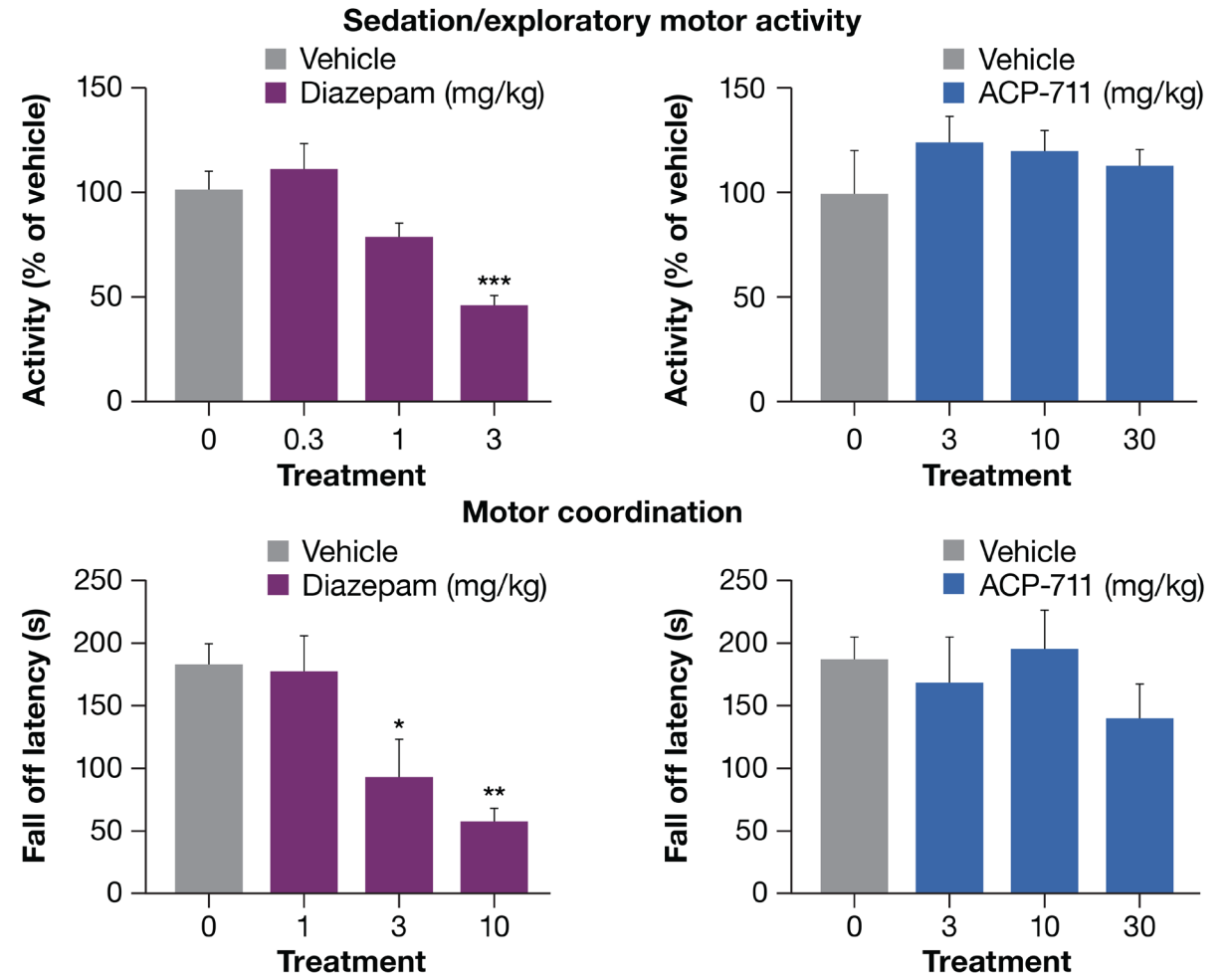
Values shown in the graph are means $\pm$ SEM. Motion power percentage is defined as the ratio of energy spent on tremor-like behavior divided by overall motion. A higher motion power percentage indicates worse tremors, with propranolol used as an active control for tremor reduction. Schematic created in BioRender. Ayala, J. (2025) <https://BioRender.com/v99zntu>.

* $P < 0.05$, ** $P < 0.01$, and **** $P < 0.0001$ vs vehicle.

ACP-711 – No Impact on Sedation/Exploratory Motor Activity and Motor Coordination in Rats



- **ACP-711 did not significantly affect exploratory motor activity or motor coordination, in contrast to diazepam**



Values shown in the graphs are means $\pm$ SEM. All substances administered orally. A decrease in exploratory motor activity relative to vehicle indicates sedative effects. A reduced time for rats to fall off the RotaRod (fall-off latency) indicates reduced motor coordination. Schematic created in BioRender. Ayala, J. (2025) <https://BioRender.com/v99zntu>.

* $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ vs vehicle.

Summary and Conclusions

ACP-711 (SAN711)

- Is a novel selective modulator of GABA_ARs containing the α_3 subunit
- Shows effectiveness in treating harmaline-induced tremors with no detectable safety signals at doses up to 30 mg/kg
- **Demonstrates potential as a safe and effective treatment option for essential tremor; further studies are warranted**

Thank you!

Questions?

