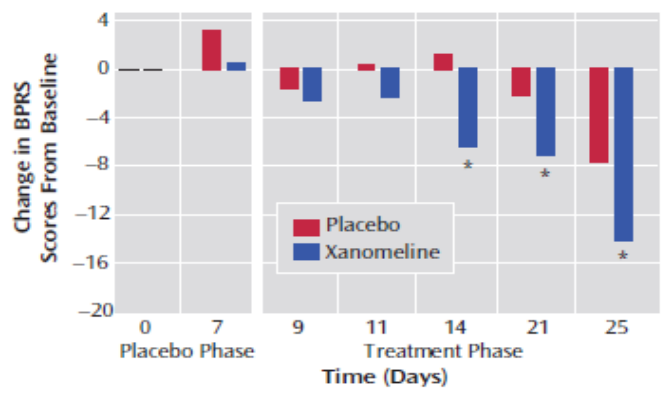
M4/M1 agonist Xanomeline: Compelling Clinical Activity, Limited by Side Effect Profile

Xanomeline (Non-selective Agonist) Impacted Symptoms…

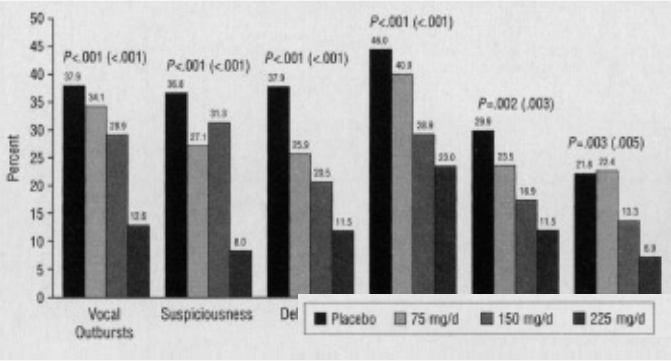
2008 Phase 2 in Schizophrenia

Statistically significant impact on total BPRS and PANSS scores in schizophrenia patients[1]



1997 Phase 2 in Alzheimer's Disease

Statistically significant impact on agitation and other psychosis-related endpoints in Alzheimer's patients[2]



…But Development Was Limited by GI Side Effects

Table 3. Adverse Events*

Event	Placebo (n=87)	Dose† Low (n=85)	Medium (n=83)	High (n=87)	Total (N=342)	P‡
Sweating	4 (4.6)	12 (14.1)	38 (45.8)	66 (75.9)	120 (35.1)	<.001
Nausea	17 (19.5)	24 (28.2)	29 (34.9)	45 (51.7)	115 (33.6)	<.001
Vomiting	8 (9.2)	11 (12.9)	33 (39.8)	37 (42.5)	89 (26.0)	<.001
Dyspepsia	7 (8.0)	20 (23.5)	23 (27.7)	21 (24.1)	71 (20.8)	.007
Chills	1 (1.1)	8 (9.4)	22 (26.5)	32 (36.8)	63 (18.4)	<.001
Chest pain	1 (1.1)	5 (5.9)	13 (15.7)	10 (11.5)	29 (8.5)	.004
Increased salivation	0 (0)	2 (2.4)	6 (7.2)	21 (24.1)	29 (8.5)	<.001
Syncope	4 (4.6)	3 (3.5)	11 (13.3)	11 (12.6)	29 (8.5)	.03
Fecal incontinence	0 (0)	4 (4.7)	1 (1.2)	6 (6.9)	11 (3.2)	.04
Nausea and vomiting	2 (2.3)	0 (0)	1 (1.2)	7 (8.0)	10 (2.9)	.009
Dysphagia	1 (1.1)	0 (0)	2 (2.4)	6 (6.9)	9 (2.6)	.03

*Only events statistically significant at P<.05 are given. Values are number (percentage) of patients unless otherwise indicated.
†Low-dose group received 25 mg of xanomeline tartrate 3 times a day; medium, 50 mg 3 times a day; high, 75 mg 3 times a day.
‡Pearson χ^2 test.

Xanomeline's high rate of nausea, vomiting and dyspepsia is likely driven by non-selective muscarinic agonism

Mechanism Supported by Phase 2 Data for KarXT

- Karuna is developing a BID fixed-dose combination of xanomeline with trospium to offset side effects of GI, dry-mouth and constipation
- In a 5-week Phase 2 study, KarXT demonstrated an 11.6 point reduction in PANSS total score from baseline vs. placebo (p<0.0001)
- Represents a robust reproduction of 2008 xanomeline Phase 2 data in schizophrenia

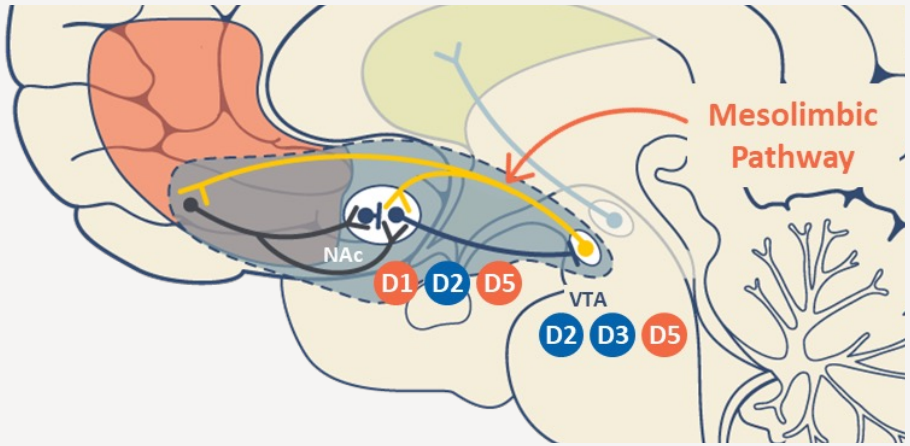
Source: 1. Shekhar et al. Am J Psychiatry, Vol 165, Aug 2008. N=20. 2 active and 3 placebo-arm patients discontinued the study, none due to adverse events.
2. Bodick et al. Arch Neurol, Vol 54, Apr 1997. N = 343. 52% of patients in high-dose arm discontinued treatment due to adverse events.

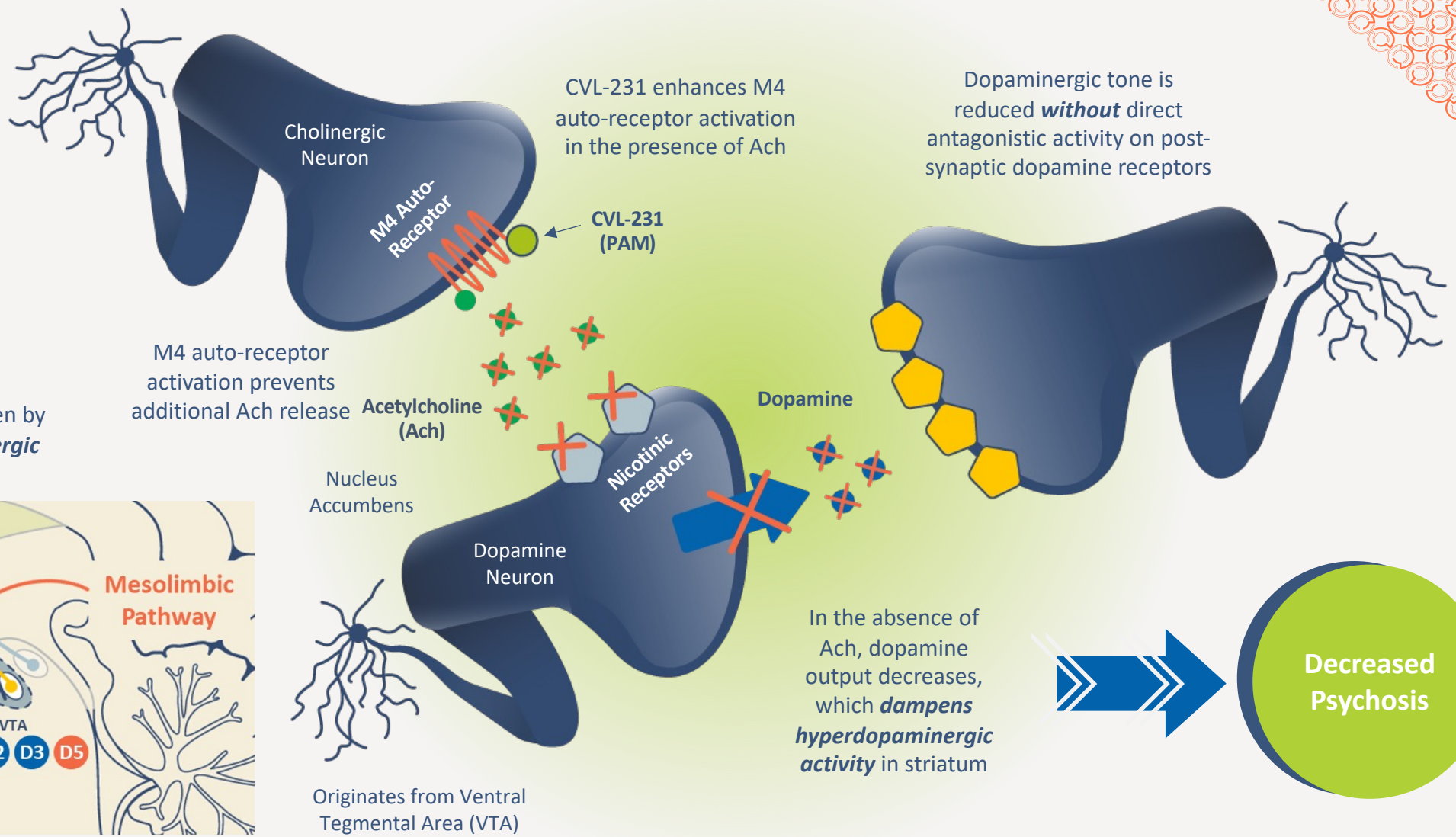
cerevel

CVL-231: M4 Receptor Activation Reduces Dopamine in the Striatum to Treat Schizophrenia

CVL-231	M4 PAM
hM4 PAM EC_{50}	12 nM
hM4 K_i	7.5 nM
Brain Availability	$C_{u,b}/C_{u,p}$ = 1
M1>833x	M2=479x
M3>833x	M5>833x

Schizophrenia symptoms driven by ***overactivity of the dopaminergic*** mesolimbic pathway





CVL-231 enhances M4 auto-receptor activation in the presence of Ach

Dopaminergic tone is reduced ***without*** direct antagonistic activity on post-synaptic dopamine receptors

M4 auto-receptor activation prevents additional Ach release

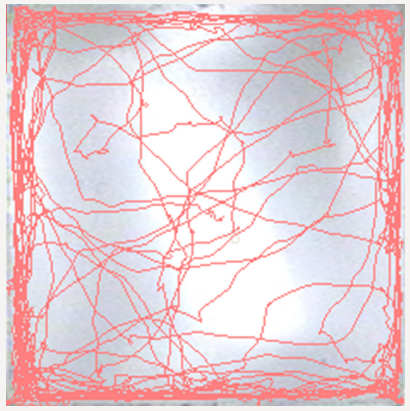
In the absence of Ach, dopamine output decreases, which ***dampens hyperdopaminergic activity*** in striatum

Decreased Psychosis

Originates from Ventral Tegmental Area (VTA)

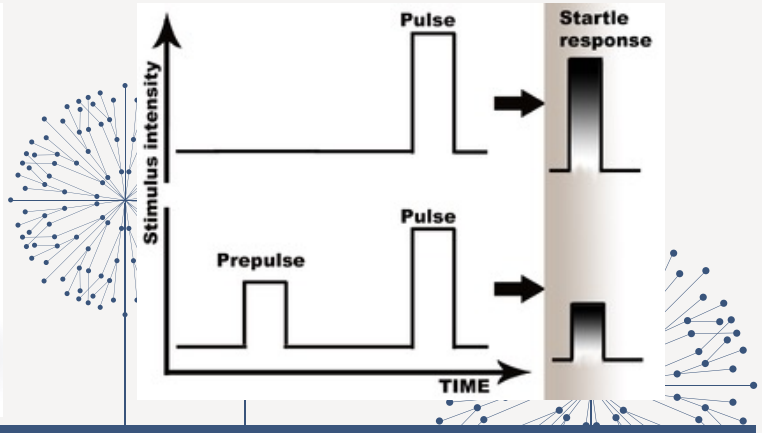
Amphetamine-stimulated locomotor activity (aLMA) methods

- Locomotor activity is recorded by sets of 16 infrared light beams which create a grid across the bottom of the open field chamber
- Following room acclimation, mice (n=10) were individually introduced into the LMA chamber and allowed to habituate for 90 minutes
- After habituation, mice were dosed with amphetamine or saline (IP) and CVL-231, Haldol, or vehicle (SC) and tested for 90 minutes
- Total distance traveled (cm) was recorded in 10-minute bins and analyzed using R statistical software



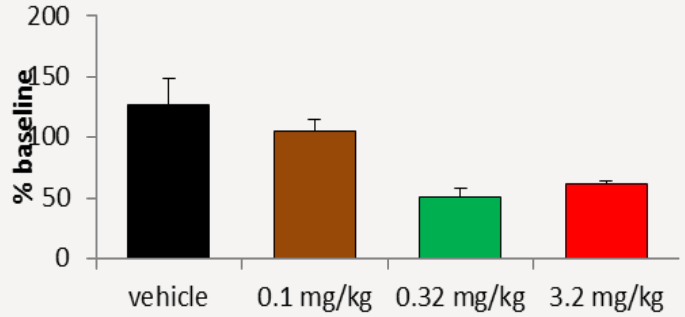
Amphetamine-stimulated prepulse inhibition of acoustic startle (aPPI) methods

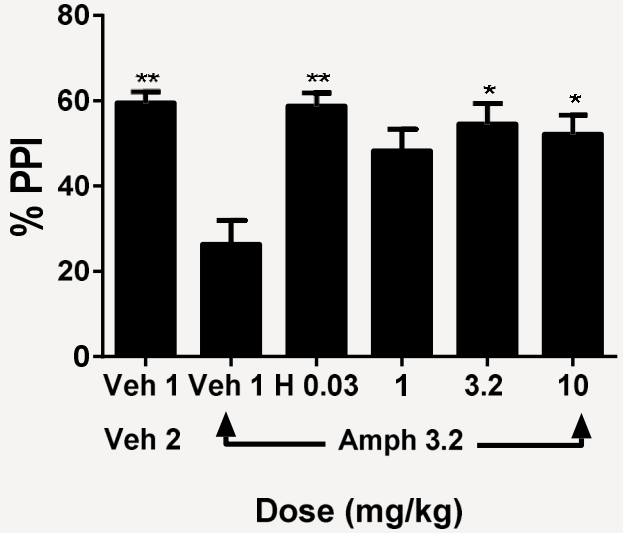
- Startle responses, with the presence or absence of a prepulse were tested and recorded using a Med Associates Startle Monitor System
- After habituation, rats (n=12) were dosed with amphetamine or saline (IP; 10 min prior to testing) and CVL-231, Haldol, or vehicle (SC; 30min prior to testing) and individually placed into startle monitor chambers
  - 5 min habituation to background noise (67dB) session → 5 pulse (120dB) alone sessions → 7 randomized trials of pulse alone, background noise, prepulse (72, 77, or 82dB) alone, prepulse + startle
- % PPI = 100 X [(Mean startle response for Pulse-only trials − Mean startle response for Prepulse/Pulse trials)] / Mean startle response for Pulse-only trials; Data was analyzed with GraphPad Prism software



Rationale for Antipsychotic Efficacy Associated with M4 Activation

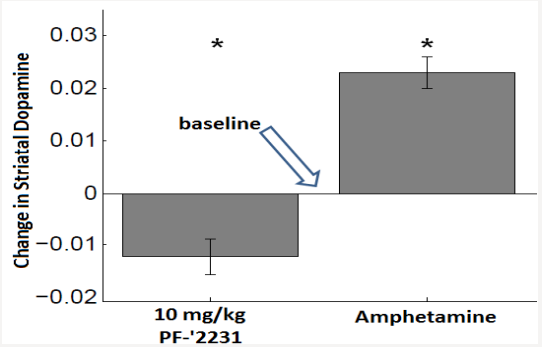
CVL-231 Attenuates Striatal Ach Release from Cholinergic Interneurons



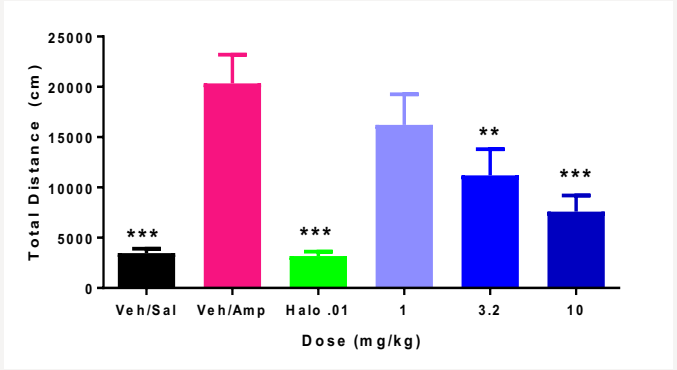


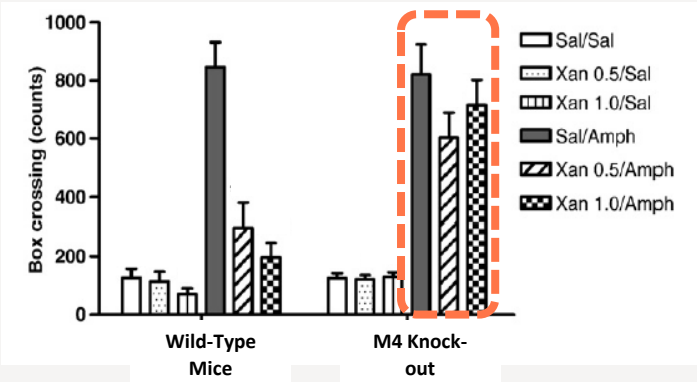
Effect of CVL-231 and Haloperidol on reversing Amphetamine-disrupted prepulse inhibition (PPI) in Rats

Through Modulation of Ach, CVL-231, Can Attenuate Striatal DA Release (Fiber photometry)



Impact of CVL-231 on Striatal Neurotransmitters Leads to Antipsychotic Efficacy



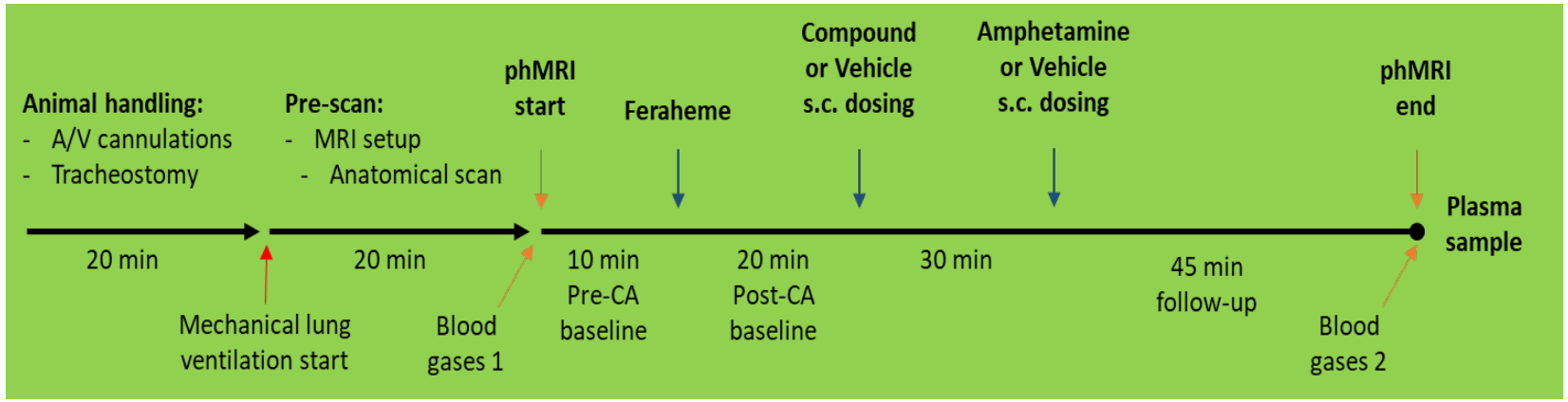


Xanomeline had no antipsychotic effect in M4 knock-out mice

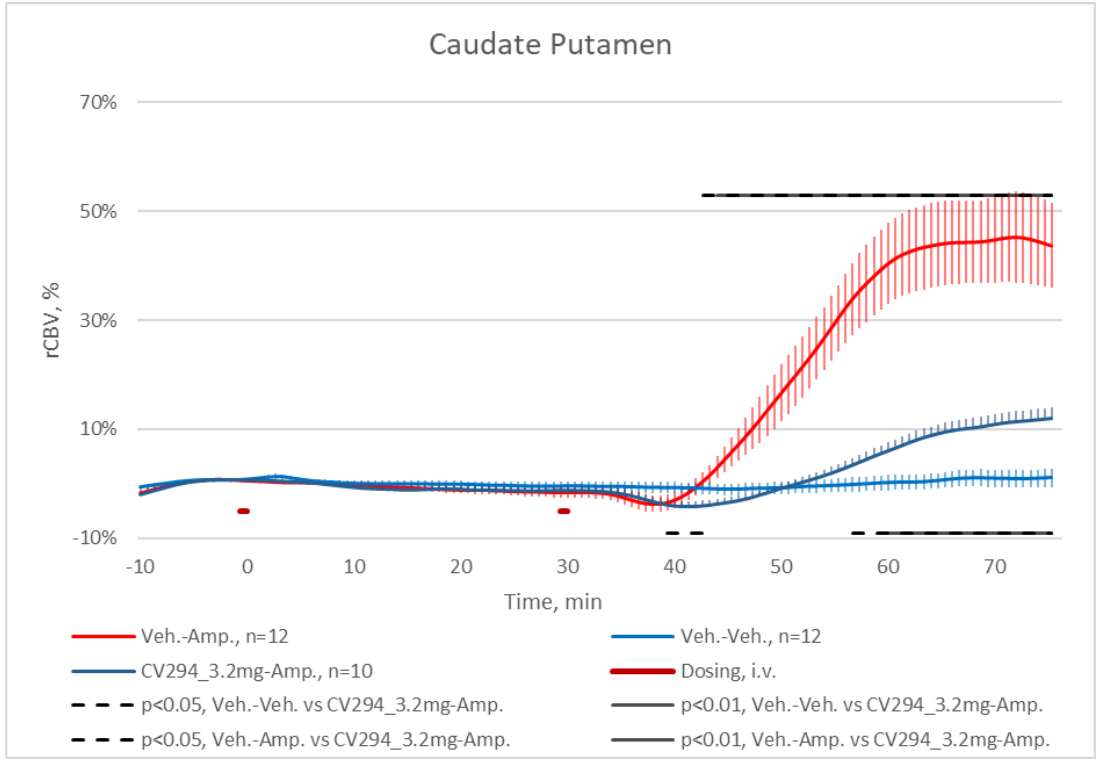
Source: Woolley, et al. European Journal of Pharmacology 603 (2009)

Further Expanding Mechanistic Understanding of M4 Activators Following Amphetamine Stimulation Using Pharmacological MRI

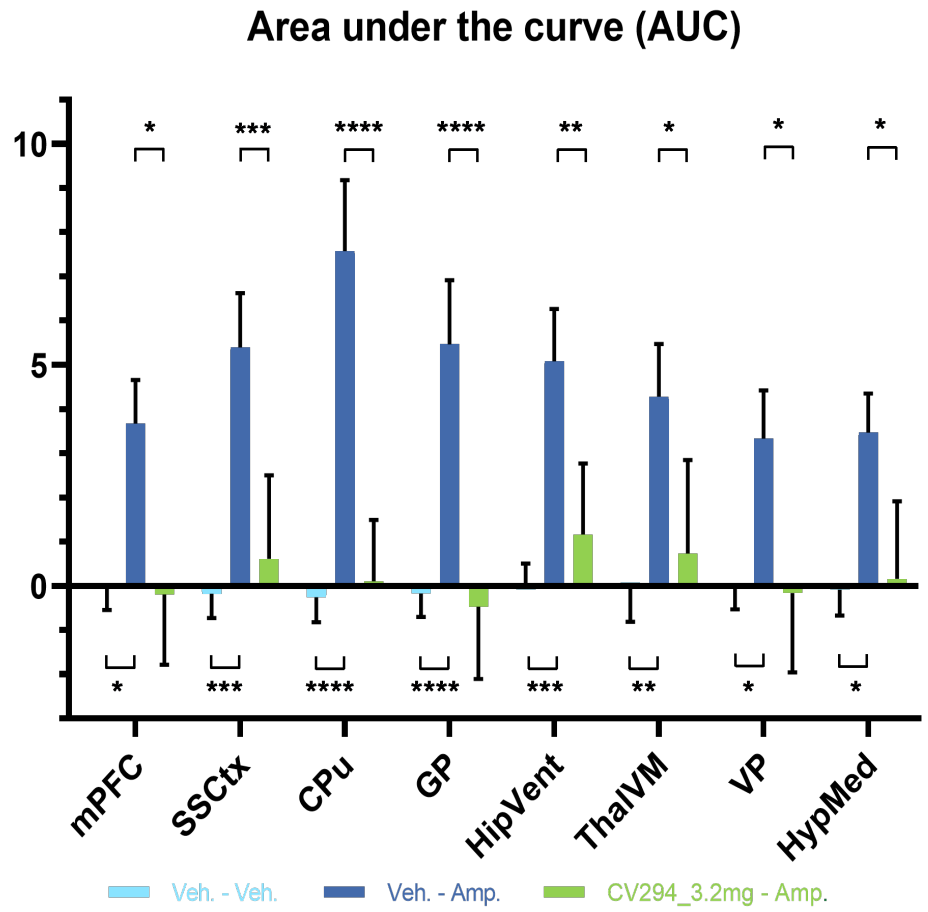
- Data were collected in medetomidine-isoflurane anesthetized Sprague-Dawley rats using relative cerebral blood volume (rCBV) pharmacological MRI (phMRI) readout at Bruker 7T MRI system
- High resolution T2*-weighted gradient-echo sequence (FLASH) was used for rCBV data collection with iron oxide contrast agent (Feraheme) injected intravenously to produce the rCBV weighting of the imaging sequence.
- Test compounds were administered subcutaneously, during uninterrupted phMRI imaging session 30 mins prior to the amphetamine dosing with 45 mins duration of the follow-up data collection after that. Plasma samples were collected at the end of the experiment.
- Studies were performed by Charles River Discovery Services Finland



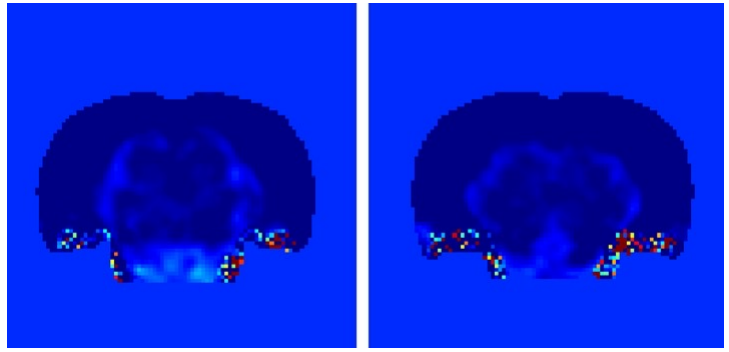
Effects of CVL-231 at 3.2 mg/kg on rCBV



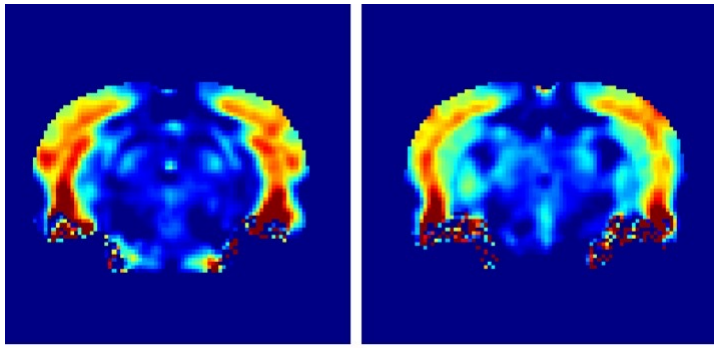
Group rCBV signal time series from **Striatum (caudate putamen)**. Data are presented as mean ± SEM. Statistical significances between groups: dashed black line $p < 0.05$; solid black line $p < 0.01$; (point-wise one-way ANOVA).



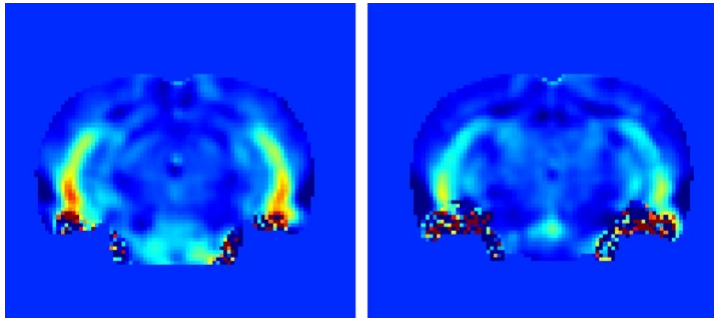
Representative Images



Vehicle



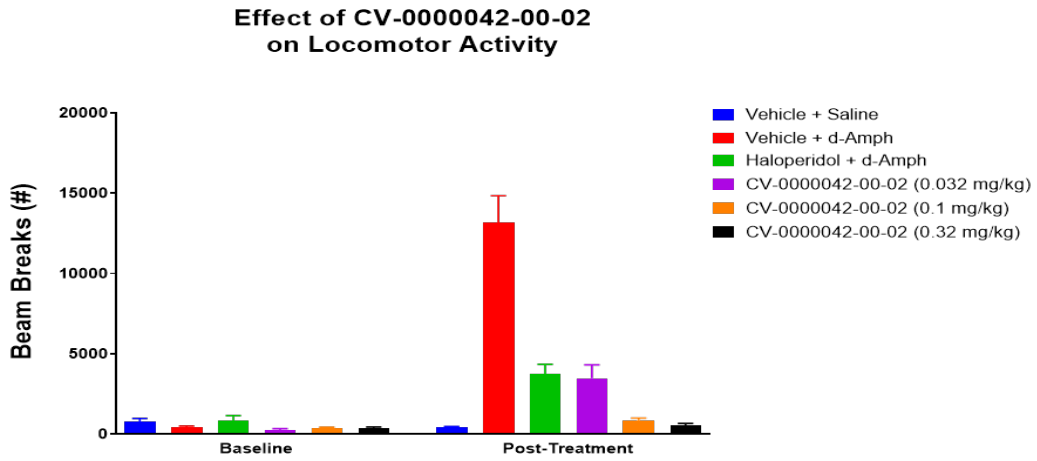
Amphet 1mg/kg



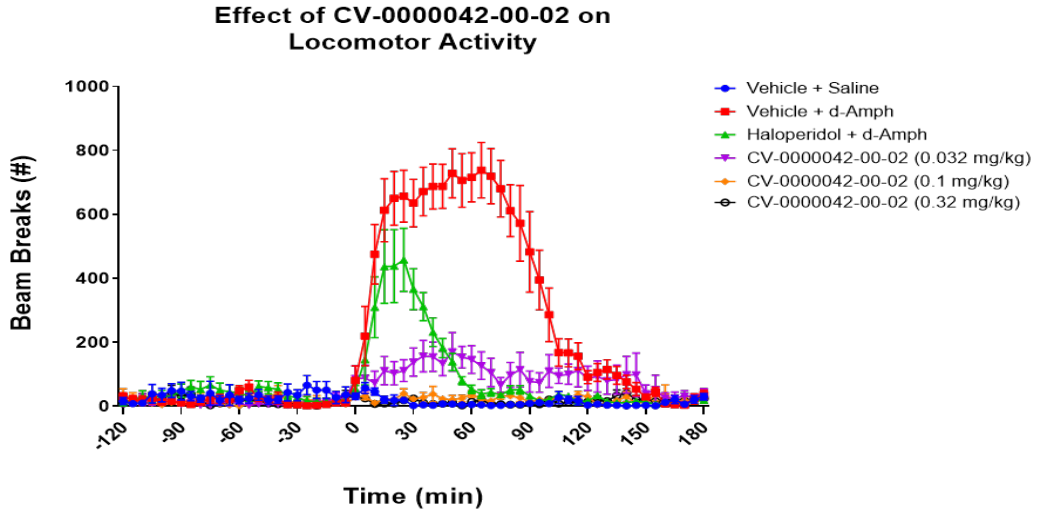
Amphet/CVL-231 3.2mg/kg

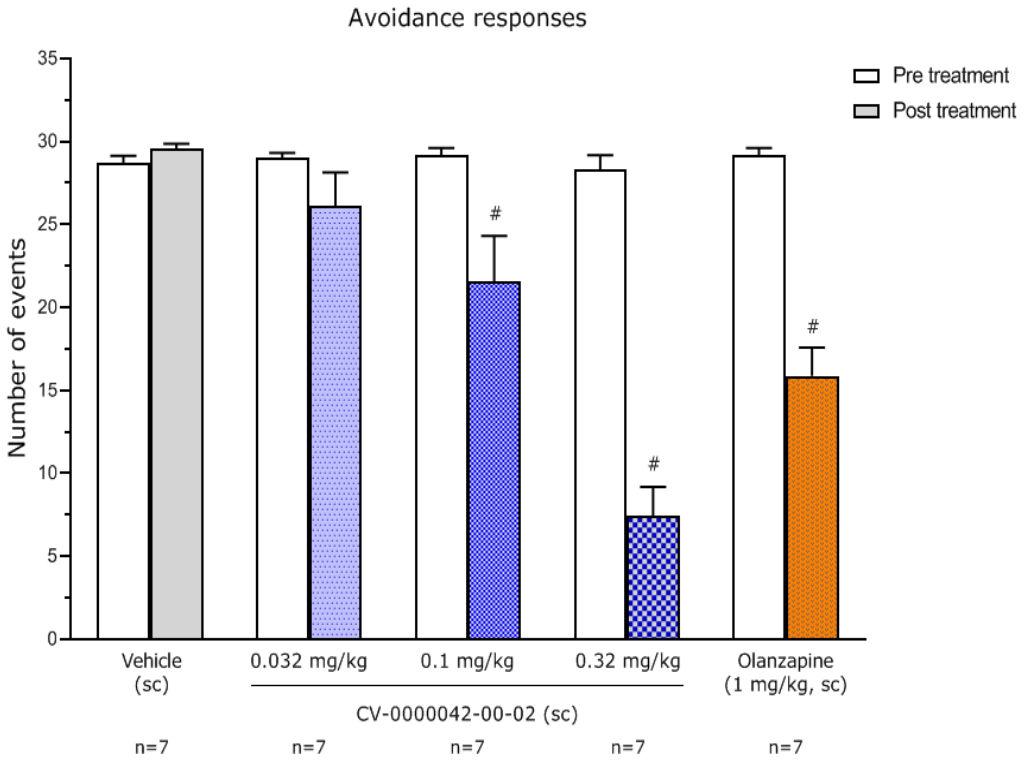
Effects of A Full M4 Agonist on Amphetamine-Stimulated Locomotion & Conditioned Avoidance Responding

A



B

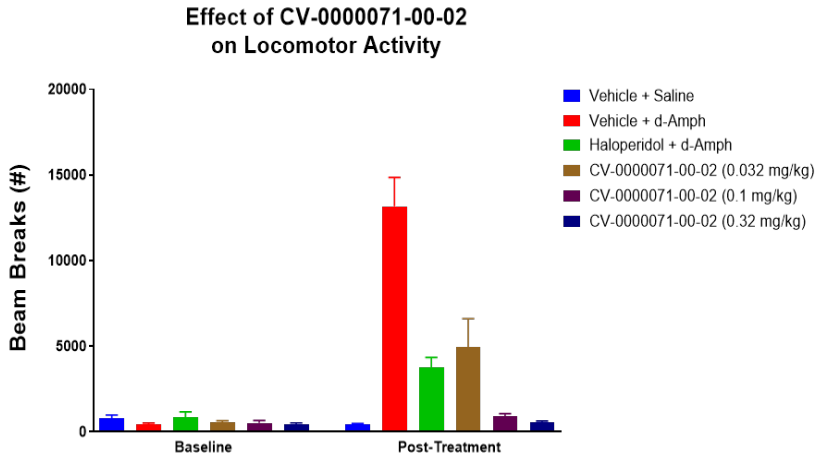




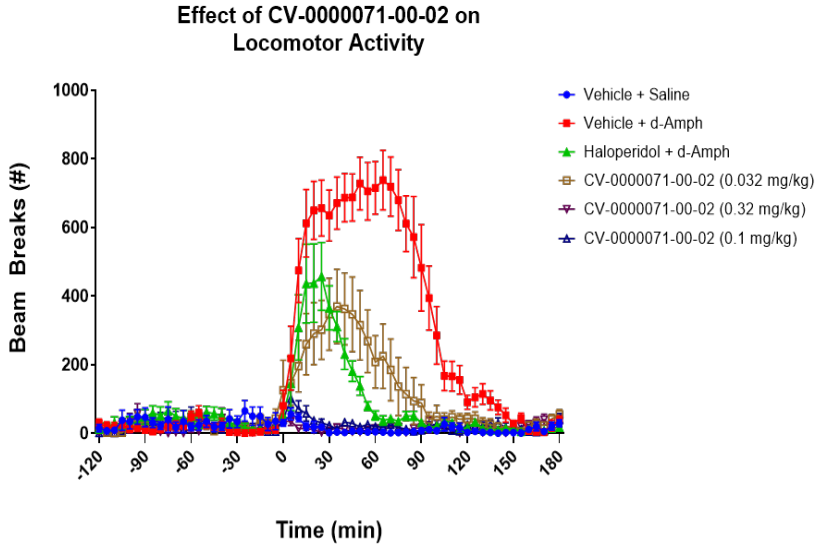
A rat is placed in a two-compartment shuttle box where a neutral conditioned stimulus (CS, auditory or visual) is presented and, after a short delay, is followed by an aversive unconditioned stimulus (US, weak foot-shock). The animal may escape the US by switching compartment. Training (performed by repeating presentations of CS-US pair) will lead to avoidance of the US i.e. the rat will switch compartment during the CS and before the onset of the US. Studies performed by Biotrial

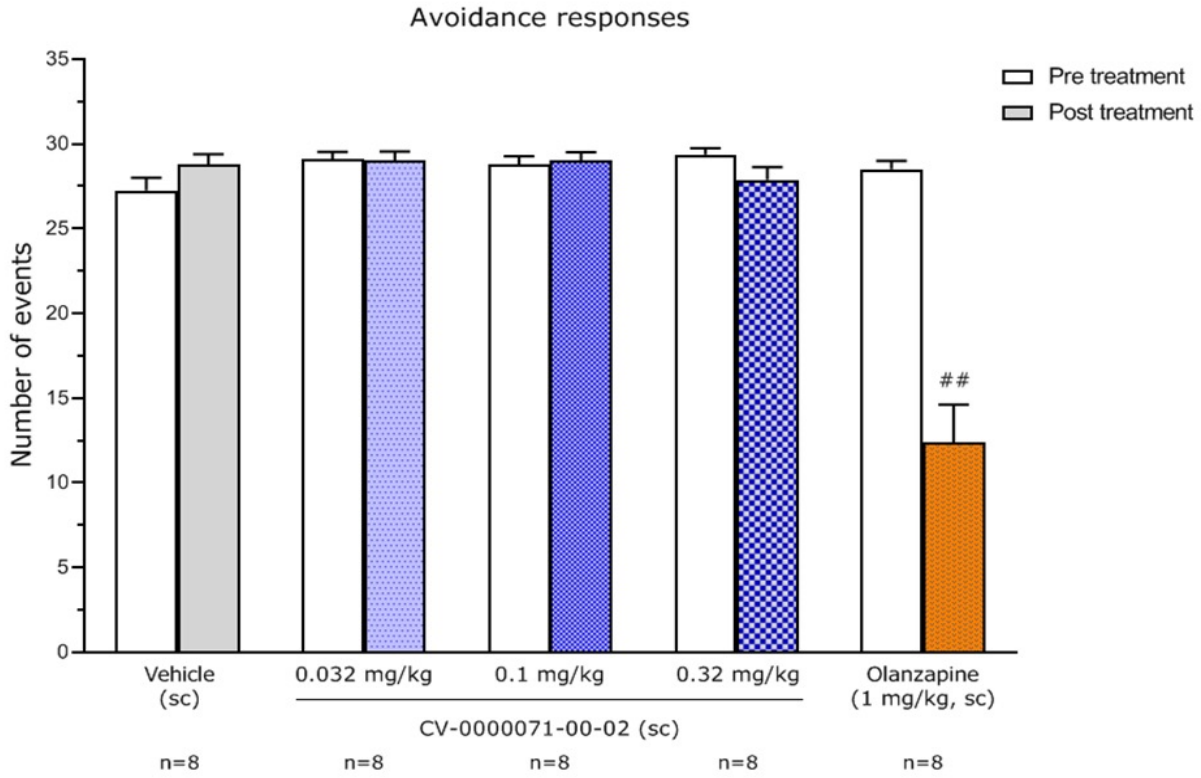
Effects of A Full M4 Partial Agonist on Amphetamine-Stimulated Locomotion & Conditioned Avoidance Responding

A



B





Conclusions

- CVL-231 a positive allosteric modulator is active in a range of preclinical models linked to psychosis
- CV 042 a full agonist at the M4 receptor is active in both amphetamine-stimulated locomotor studies and conditioned avoidance responding
- CV 071 a partial agonist at the M4 receptor is active in amphetamine-stimulated locomotor studies but NOT conditioned avoidance responding
- The results suggest that each mechanism of activation may provide a unique profile that could make it better suited to the treatment of the symptoms associated with a particular CNS disorder