PHARMACODYNAMIC EFFECTS OF THE P2X7 RECEPTOR ANTAGONIST JNJ-54175446 IN A TRANSLATIONAL HUMAN DEXAMPHETAMINE CHALLENGE MODEL

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INTRODUCTION

JNJ-54175446 (JNJ) is a selective, potent, brain penetrant antagonist of the P2X7 ion channel (P2X7R). The central P2X7R is involved in neural-glia interactions and activation is associated with the production of the cytokine interleukin-1β. In rodents, JNJ attenuates lipopolysaccharide/BzATP-induced increases in interleukin-1β levels and attenuates amphetamine-induced increases in locomotion. The objective of the current proof-of-mechanism study was to investigate the pharmacodynamic (PD) effects of JNJ at steady-state, using an acute dexamphetamine (AMPH) challenge.

METHODS

- 64 healthy male volunteers (age 18-55) participated in a double-blind, placebo-controlled, multiple ascending dose study. 48 subjects were randomised to one of 6 treatments: JNJ (n=6 on 50 and 100mg; n=12 on 150, 300 and 450mg) or placebo (n=16).
- Subjects underwent an unblinded baseline oral 20 mg AMPH challenge at day -5, followed by 11 consecutive days q.d. dosing with JNJ/placebo, with a cross-over AMPH/placebo challenge on days 7 and 10 (Figure 1). On challenge days, NeuroCart PD tests (listed in Table 1) were repeated 4 times pre- and post-challenge.
- A mixed model ANOVA was used with the average pre-AMPH values of day -5 as a covariate. Post-AMPH values of day -5 were subtracted from day 7/10 post-AMPH/placebo.

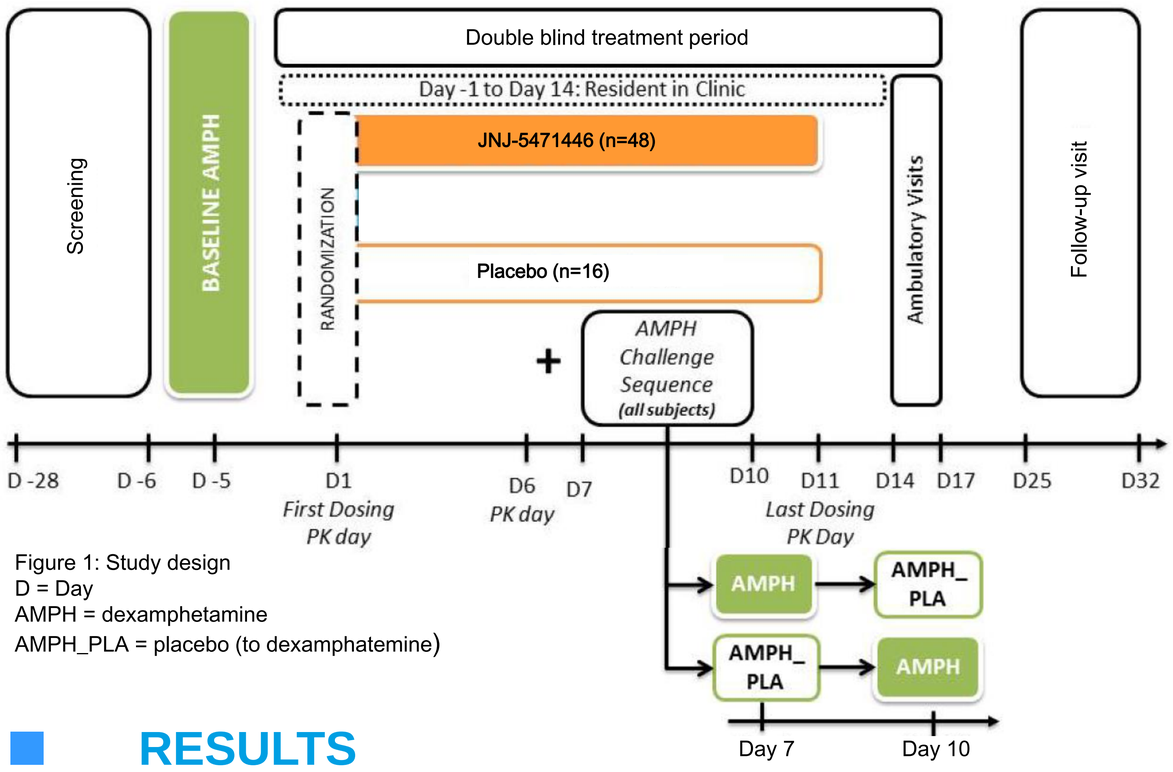

Figure 1: Study design
D = Day
AMPH = dexamphetamine
AMPH_PLA = placebo (to dexamphatemine)

RESULTS

At steady state, JNJ by itself caused moderate decreases of finger tapping, adaptive tracking and saccadic reaction time compared to placebo (p-values reported in table 1). JNJ did not affect saccadic peak velocity, smooth pursuit eye movements, body sway or subjective effects (VAS). On day -5, unblinded AMPH stimulated a wide range of subjective and performance tests, akin to results from a previous AMPH study [1]. Repetition of the AMPH challenge on day 7 or 10 in the placebo group showed similar AMPH effects as on day -5 (e.g. Figure 2 for adaptive tracking).

JNJ ameliorated AMPH-induced increases of finger tapping (at ≥300mg) and adaptive tracking (at 300mg, Figure 3). JNJ enhanced subjective effects of AMPH on VAS mood (at 100mg and 150mg) and VAS feeling high (at ≥300mg). AMPH-induced cortisol elevations were also increased by JNJ (at ≥300mg). JNJ was well-tolerated at all dose levels tested.

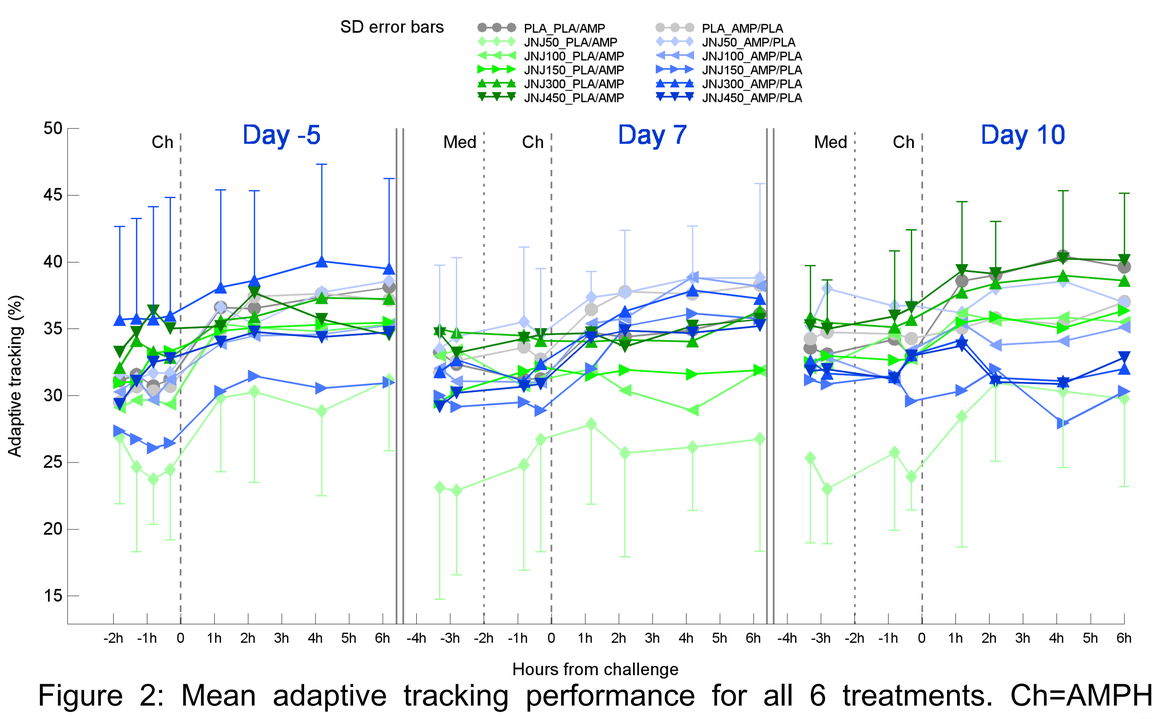

Figure 2: Mean adaptive tracking performance for all 6 treatments. Ch=AMPH challenge. Green lines represent subjects who received AMPH_placebo on day 7 and blue received AMPH_placebo on day 10. Med=dosing of JNJ or placebo.

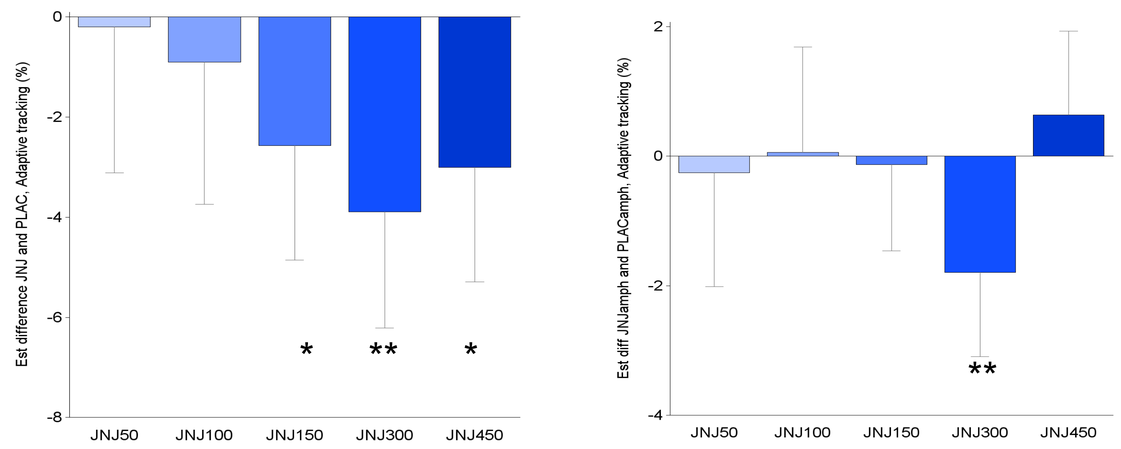

Figure 3: Adaptive tracking performance of the JNJ groups relative to the placebo group, after the AMPH_placebo challenge (left) and AMPH challenge (right).

NeuroCart test	JNJ vs Placebo following AMPH_Placebo challenge		JNJ vs Placebo following AMPH challenge (day -5 corrected)	
Saccadic reaction time (RT)	JNJ150 > Plac JNJ300 > Plac JNJ450 > Plac	P=0.033 P=0.020 P=0.014	N.s.	
Saccadic velocity	JNJ50 < Plac	P=0.020	JNJ50+Amph < Plac+Amph	P<0.001
Saccadic inaccuracy	N.s.		JNJ100+Amph < Plac+Amph	P=0.035
Adaptive tracking	JNJ150 < Plac JNJ300 < Plac JNJ450 < Plac	P=0.028 P=0.001 P=0.011	JNJ300+Amph < Plac+Amph	P=0.007
Finger tapping	JNJ150 < Plac JNJ450 < Plac	P=0.040 P=0.017	JNJ300+Amph < Plac+Amph JNJ450+Amph < Plac+Amph	P=0.013 P<0.001
Body Sway	N.s.		N.s.	
VAS Calmness	N.s.		JNJ300+Amph > Plac+Amph	P=0.004
VAS Feeling high	N.s.		JNJ300+Amph > Plac+Amph JNJ450+Amph > Plac+Amph	P=0.011 P=0.001
VAS Mood	N.s.		JNJ100+Amph > Plac+Amph JNJ150+Amph > Plac+Amph	P=0.006 P=0.003
Stop signal RT	JNJ300 > Plac	P=0.04	JNJ450+Amph > Plac+Amph	P<0.001
Cortisol	JNJ300 > Plac	P=0.001	JNJ300+Amph > Plac+Amph JNJ450+Amph > Plac+Amph	P=0.012 P<0.001

Table 1: P-values (<0.05) of the estimates of the difference between the Least Squares Means of contrasts for the 6 treatment groups. N.s.=not significant.

CONCLUSIONS

This is the first report of the PD effects of the central P2X7R antagonist JNJ in humans. At steady-state plasma concentrations, JNJ dose-dependently increased saccadic RT and reduced performance on (visuo)motor tests. Similar to results from animal models, JNJ attenuated AMPH-induced improvements of motor performance. Mood elevating effects of AMPH were enhanced by JNJ. Our findings support the theory that P2X7R antagonism modulates excitatory neurotransmission, possibly through a reduction in glutamatergic signaling [2].

[1] Van der Aart et al. 2016, Amphetamine Induced Psychomotor Improvement in Relation to Striatal Dopamine Release in Healthy Subjects. JCBFM:36, p735-6.

[2] Iwata et al. 2016, Psychological Stress Activates the Inflammasome via Release of ATP and Stimulation of the Purinergic Type 2X7 Receptor. Biol Psychiatry:80(1) p12-22.

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