

**Abuse-Related Effects of Dual Dopamine/Serotonin Releasers
with Varying Potency to Release Norepinephrine in Male Rats and Rhesus Monkeys**

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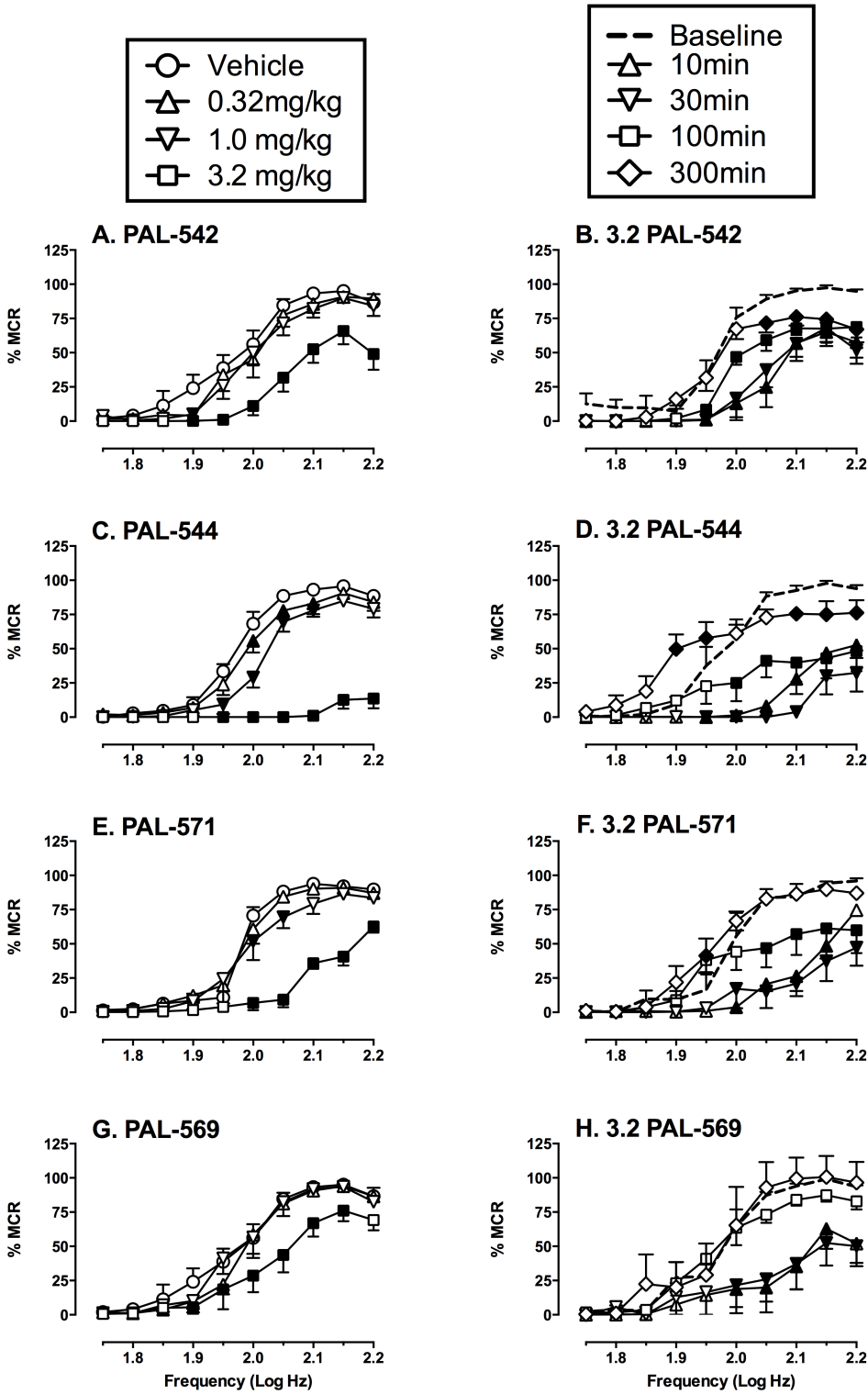


Figure 1: Effects of PAL-542, PAL-544, PAL-571, and PAL-569 in an assay of intracranial self-stimulation in rats. Left panels (A, C, E, and G) show drug effects on full ICSS frequency-rate curves.

Right panels (B, D, F, and H) show time course of effects produced by 3.2 mg/kg of each compound. Abscissae: Frequency of electrical brain stimulation in Log Hz. Ordinates: percent maximum control reinforcement rate (%MCR). All symbols represent mean \pm s.e.m. of 5 rats. Filled symbols represent frequencies at which reinforcement rates were statistically different ($p < 0.05$) from vehicle (A, C, E G) or baseline (B, D, F, H). PAL-542 produced significant rate-decreasing effects at 1.9 log Hz after 0.32 and 1.0 mg/kg and at 1.9-2.2 log Hz after 3.2 mg/kg (frequency: $F(9,36) = 94.8$, $p < 0.05$; PAL-542 dose: $F(3,12) = 196$, $p < 0.05$; frequency \times PAL-542 dose: $F(27,108) = 27.7$, $p < 0.05$). PAL-544 produced significant rate-decreasing effects at 2.0-2.1 log Hz after 0.32 mg/kg, at 1.95-2.1 log Hz after 1.0 mg/kg, and at 1.95-2.2 log Hz after 3.2 mg/kg (frequency: $F(9,36) = 91.1$, $p < 0.05$; PAL-544 dose: $F(3,12) = 16.5$, $p < 0.05$; frequency \times PAL-544 dose: $F(27,108) = 2.8$, $p < 0.05$). PAL-571 produced significant rate-decreasing effects at 2.0-2.05 log Hz after 1.0 mg/kg and at 2.0-2.2 log Hz after 3.2 mg/kg (frequency: $F(9,36) = 133.8$, $p < 0.05$; PAL-571 dose: $F(3,12) = 35.3$, $p < 0.05$; frequency \times PAL-571 dose: $F(27,108) = 8.9$, $p < 0.05$). PAL-569 produced significant rate-decreasing effects at 1.9-2.15 log Hz after 3.2 mg/kg (frequency: $F(9,36) = 103.2$, $p < 0.05$; frequency \times PAL-569 dose: $F(27,108) = 1.8$, $p < 0.05$). PAL-542 produced significant rate-decreasing effects from 10-300 min (frequency: $F(9,36) = 61.2$, $p < 0.05$; time: $F(4,16) = 18.7$, $p < 0.05$; frequency \times time: $F(36,144) = 3.9$, $p < 0.05$). Both PAL-544 (frequency: $F(9,36) = 36.8$, $p < 0.05$; time: $F(4,16) = 25.2$, $p < 0.05$; frequency \times time: $F(36,144) = 7.7$, $p < 0.05$) and PAL-571 (frequency: $F(9,36) = 77.0$, $p < 0.05$; time: $F(4,16) = 8.5$, $p < 0.05$; frequency \times time: $F(36,144) = 8.5$, $p < 0.05$) produced rate-increasing effects at 100 min and a mixed profile of rate-increasing and rate-decreasing effects at 300 min, with rate-increasing effects apparent at intermediate frequencies (1.9-1.95 log Hz for PAL-544 and 1.95 log Hz for PAL-571), and rate-decreasing effects at high frequencies (2.1-2.2 log Hz for PAL-544 and 2.05-2.2 log Hz for PAL-571). In contrast to the longer duration of action of the other compounds,

PAL-569 rate-decreasing effects were no longer significant at 100 min (frequency: $F(9,36) = 48.6, p < 0.05$; time: $F(4,16) = 3.4, p < 0.05$; frequency \times time: $F(36,144) = 2.3, p < 0.05$).

Table 1: Number of rats earning at least one reinforcer (numerator) in each group of animals (N=denominator) for each drug dose (mg/kg) and pretreatment time. These data represent the number of rats contributing to the data points in Figures 1A, 1C, 2A, and 2C below. Time courses were conducted using the highest dose tested. Shading indicates reference compounds.

Drug	Unit Drug Dose (mg/kg, IP)					Pretreatment Time (min)			
	0.1	0.32	1.0	3.2	5.6	10	30	100	300
Amphetamine	6/6	6/6	5/6	--	--	5/5	5/5	5/5	5/5
PAL-287	--	5/5	5/5	5/5	0/5	0/5	5/5	5/5	5/5
Fenfluramine	--	6/6	6/6	6/6	--	6/6	3/6	1/6	6/6
PAL-542	5/5	5/5	5/5	3/5	--	3/5	5/5	5/5	5/5
PAL-544	--	5/5	5/5	2/5	--	2/5	1/5	1/5	2/5
PAL-571	--	6/6	6/6	5/6	--	5/6	2/6	3/6	6/6
PAL-569	5/5	5/5	5/5	4/5	--	4/5	5/5	5/5	5/5

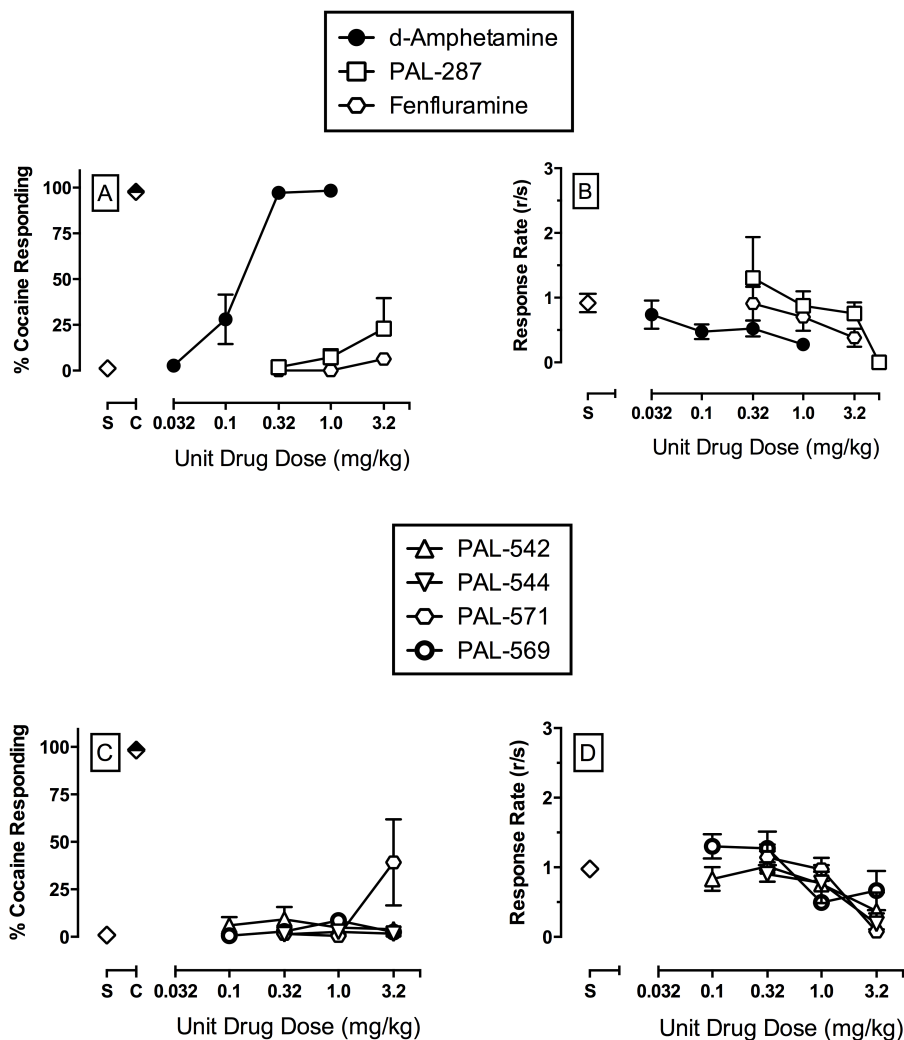


Figure 2: Dose-effect functions for the cocaine-like discriminative stimulus effects of d-amphetamine, fenfluramine, PAL-287, PAL-542, PAL-544, PAL-571, and PAL-569 in rats. Panels A and C show percent cocaine-appropriate responding as a function of unit drug dose, and Panels B and D show the corresponding rates of operant responding in responses per second. Symbols above “S” and “C” represent the group averages \pm SEM for all training sessions preceding test session when the saline- and cocaine-appropriate keys were correct, respectively. All points represent the mean \pm SEM of 5-6 rats except where indicated in Table 1 for Panels A and C. In these cases, rates of operant responding were eliminated in some rats.

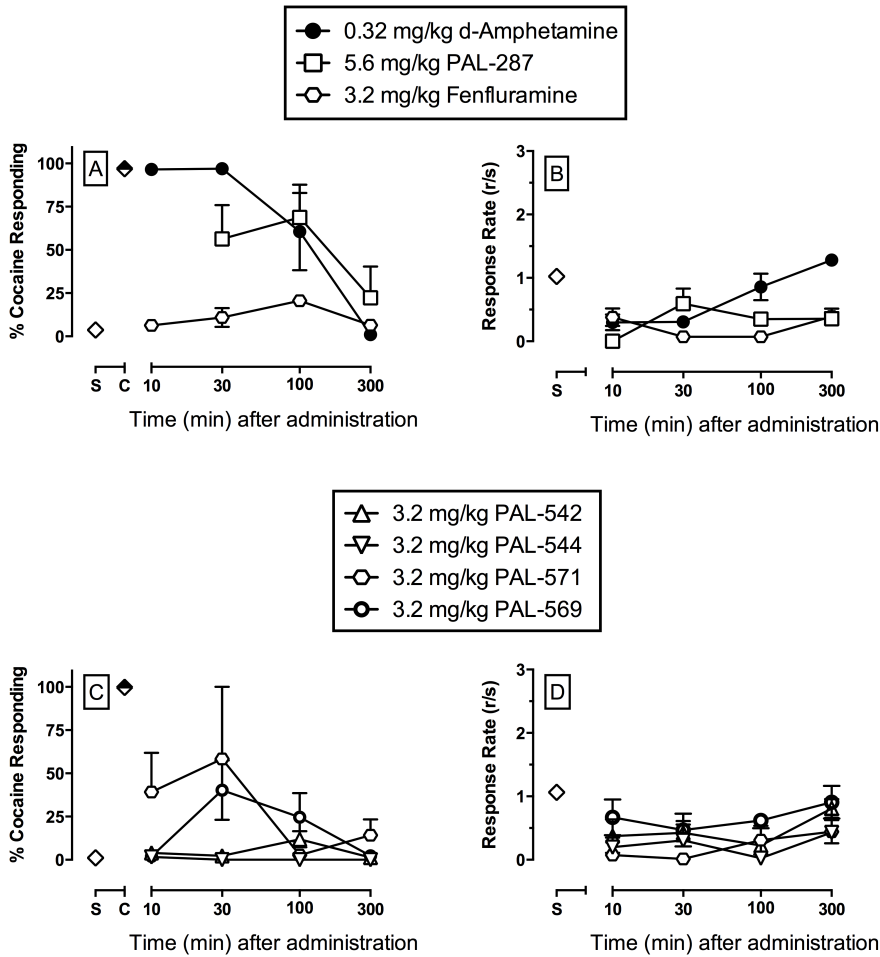


Figure 3: Time course of cocaine-like discriminative stimulus effects of d-amphetamine, fenfluramine, PAL-287, PAL-542, PAL-544, PAL-571, and PAL-569 in rats. Panels A and C show percent cocaine-appropriate responding as a function of time in minutes after drug administration, and Panels B and D show the corresponding rates of operant responding in responses per second. Symbols above “S” and “C” represent the group averages \pm SEM for all training sessions preceding test session when the saline- and cocaine-appropriate keys were correct, respectively. All points represent the mean \pm SEM of 5-6 rats except where indicated in Table 1 for Panels A and C. In these cases, rates of operant responding were eliminated in some rats.

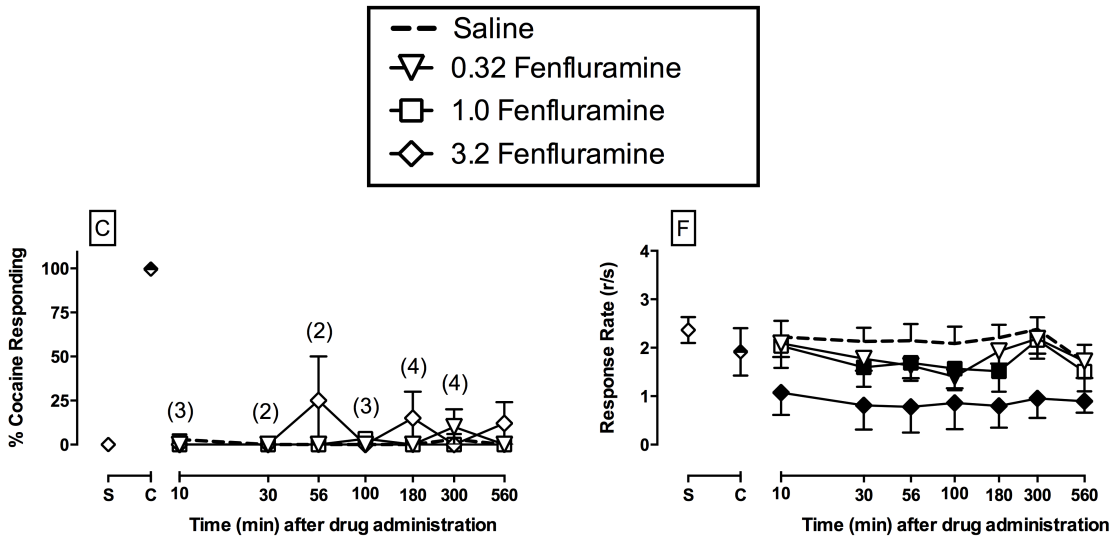
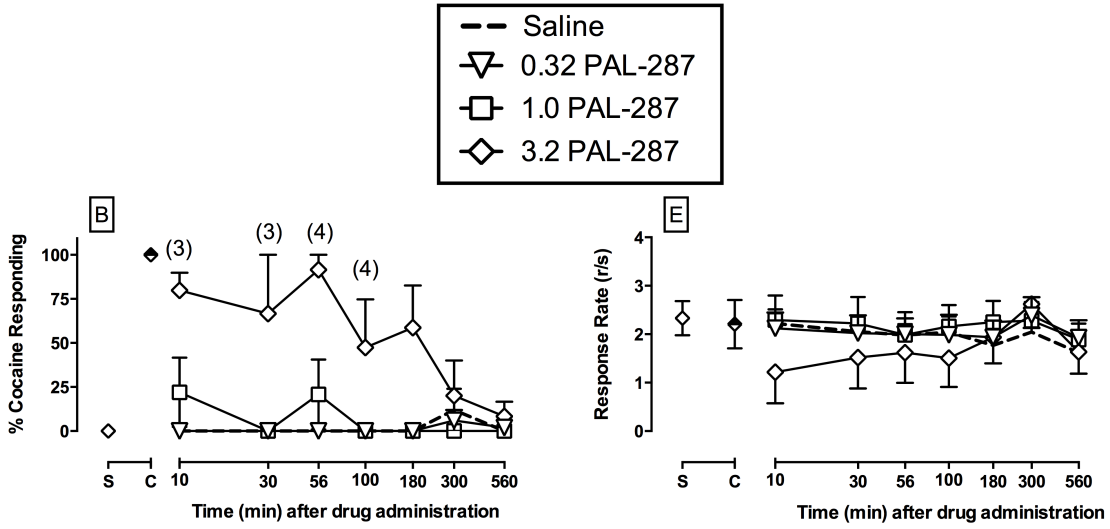
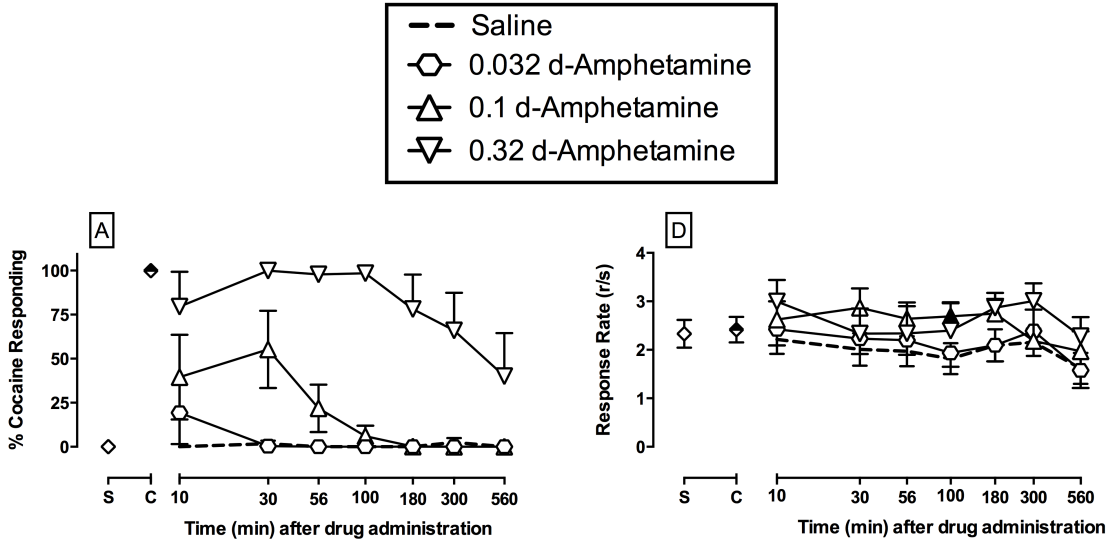


Figure 4: Time course of the cocaine-like discriminative stimulus effects for d-amphetamine (0.032 – 0.32 mg/kg, Panel A), PAL-287 (0.32 – 3.2 mg/kg, Panel B), and (±)-fenfluramine (0.32 – 3.2 mg/kg, Panel C) in rhesus monkeys (n=5). All points represent the mean \pm SEM of 5 monkeys except where indicated by numbers in parentheses in the top panels. In these cases, rates of operant responding were eliminated in some monkeys and the parenthetic number indicates the number of subjects responding at levels sufficient to contribute to the data point. Symbols above “S” and “C” represent the group averages \pm SEM for all training sessions preceding test sessions when the saline- and cocaine-appropriate keys were correct, respectively. Panels D – F show d-amphetamine, PAL-287, and fenfluramine effects on rates of operant responding, respectively.

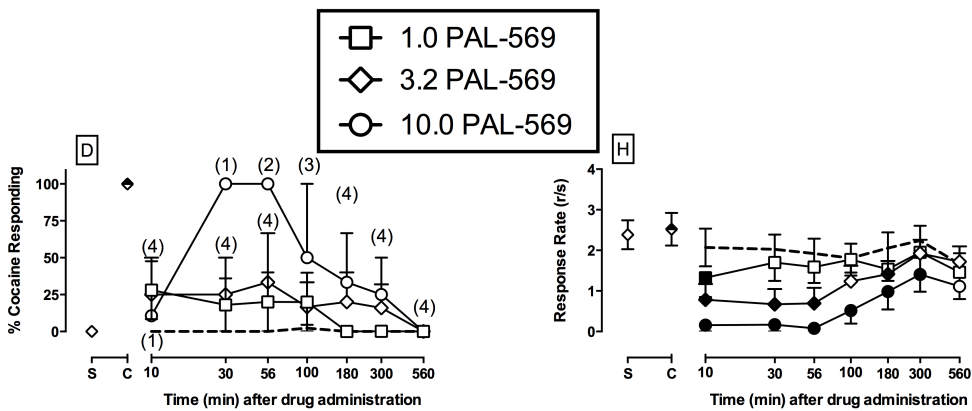
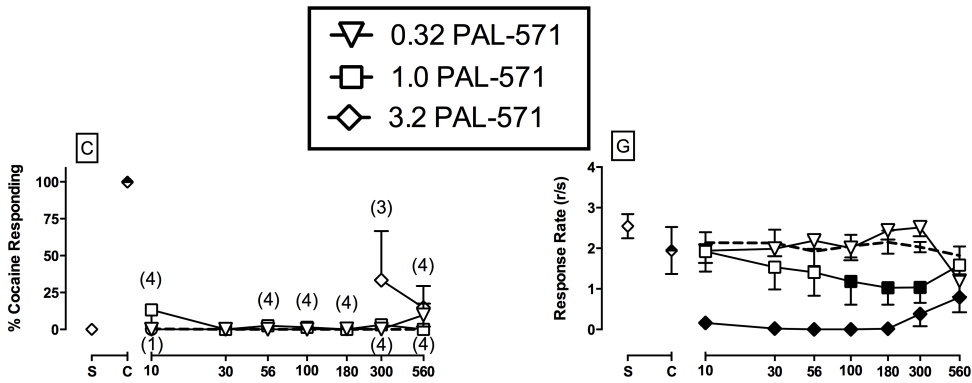
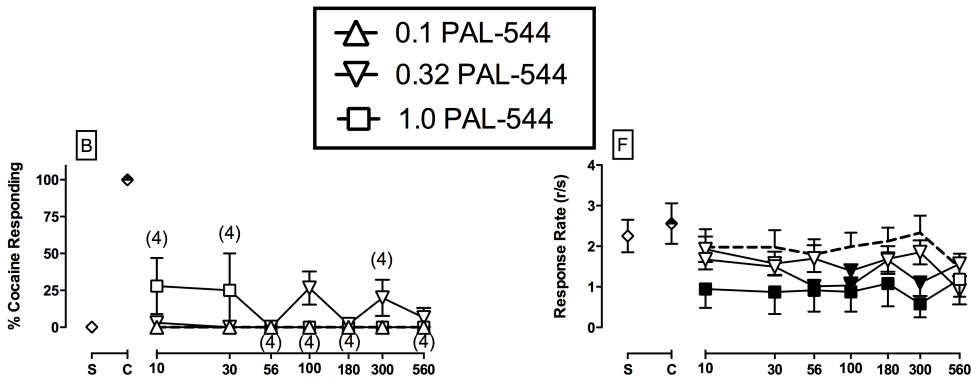
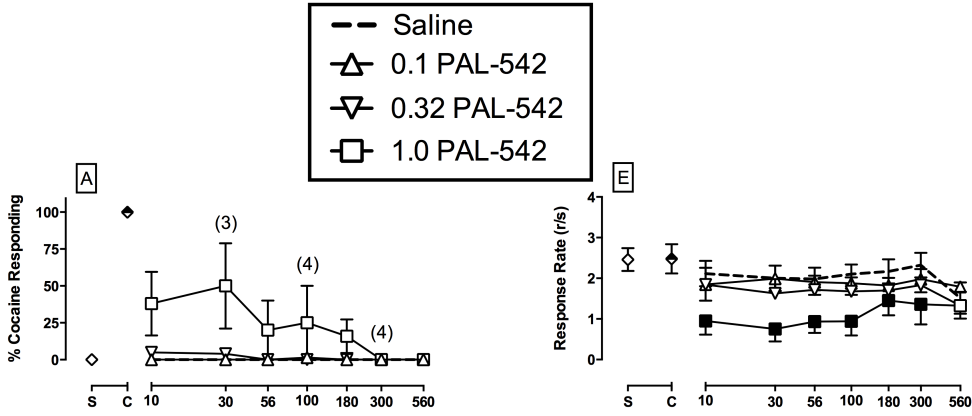


Figure 5: Time course of the cocaine-like discriminative stimulus effects of PAL-542 (0.1 – 1.0 mg/kg, Panel A), PAL-544 (0.1 – 1.0 mg/kg, Panel B), PAL-571 (0.32 – 3.2 mg/kg, Panel C), and PAL-569 (1.0 – 10.0 mg/kg, Panel D) in rhesus monkeys (n=5). All points represent the mean \pm SEM of 5 monkeys except where indicated by numbers in parentheses in the left panels. In these cases, rates of operant responding were eliminated in some monkeys, and the parenthetic number indicates the number of subjects responding at levels sufficient to contribute to the data point. Panels E – H show PAL-542, PAL-544, PAL-571, and PAL-569 effects on rates of operant responding, respectively.