Supporting Information

KVA-D-88, a novel preferable phosphodiesterase 4B inhibitor, decreases cocaine-mediated reward properties *in vivo*

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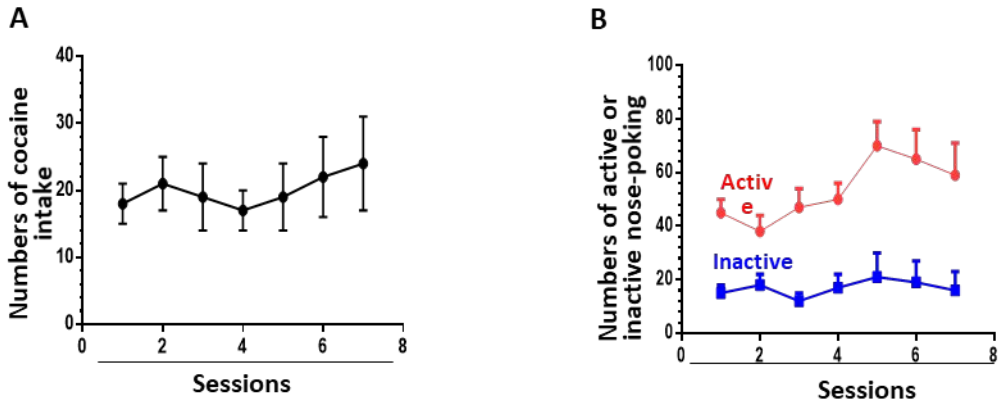
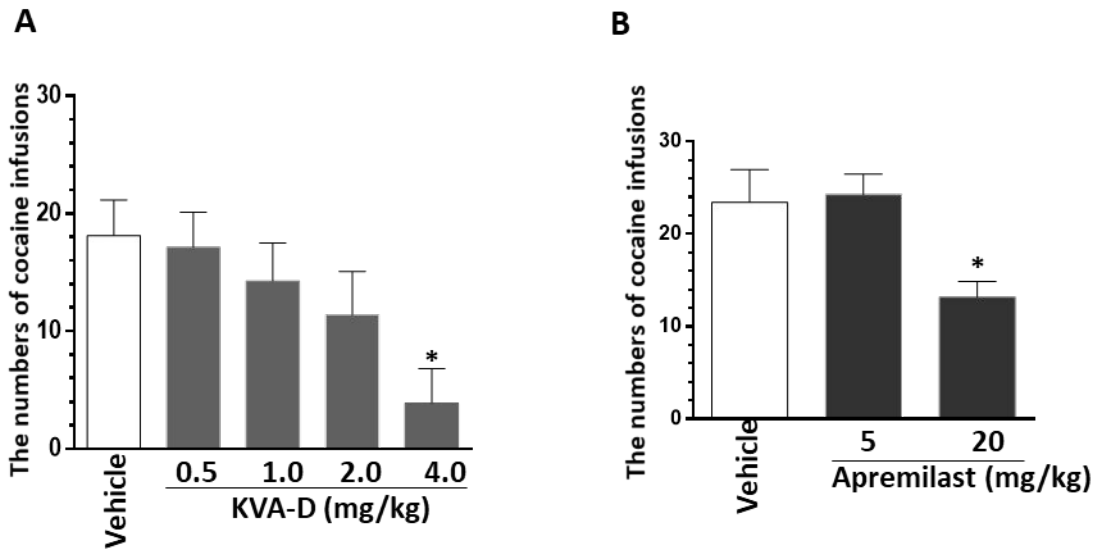
PDE	% Inhibition	PDE	% Inhibition
PDE1A1	23	PDE4D2	94
PDE1B	18	PDE4D3	79
PDE1C	15	PDE4D7	81
PDE2A1	4	PDE5A1	13
PDE3A	7	PDE6C	3
PDE3B	7	PDE7A1	1
PDE4A1A	87	PDE7B	1
PDE4A4B	88	PDE8A1	10
PDE4A10	91	PDE9A2	2
PDE4B1	81	PDE10A1	23
PDE4B2	93	PDE10A2	29
PDE4B3	91	PDE11A4	15
PDE4C1	54		

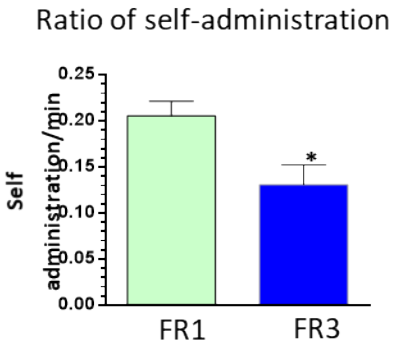
Supplementary table 1: The inhibitory effects of KVA-D-88 on PDE4 isoforms. The IC50 values of KVA-D-88 on PDE4 isoforms were determined by BPS Bioscience, San Diego.



Supplementary Fig. 1: The establishment of cocaine self-administered mice. WT mice (both genders, 3-month old) were trained to develop stable cocaine self-administration on FR1 schedule. Then mice were pre-injected with KVA-D-88 at different doses and 30 min later put into self-administration box to record the numbers of cocaine self-intake and active nose-poking. Mice with vehicle injection served as controls. (**A**) The numbers of cocaine infusions in cocaine self-administered mice at basal levels. (**B**) The numbers of active nose-poking in cocaine self-administered mice at basal levels.



Supplementary Fig. 2: The dose-curve effects of PDE4 inhibitors on cocaine self-intake. WT mice (3-month old) were trained to develop stable cocaine self-administration on FR1 schedule. Then mice were pre-injected with KVA-D-88 or apremilast at varying doses and 30 min later put into self-administration box to record the numbers of cocaine self-intake and active nose-poking. (**A**) KVA-D-88 dose-dependently decreases cocaine intake. KVA-D-88 was administered into mice with increasing dose: 0.5, 1.0, 2.0, and 4.0 mg/kg for consecutive two sessions and the numbers of active nose poke were calculated as the average for each mouse (n = 4). (**B**) Apremilast decreased the number of cocaine infusions at the dose of 20 mg/kg but not at 5 mg/kg. Apremilast was administered into mice with increasing dose: 5 and 20 mg/kg for consecutive two sessions and the numbers of active nose poke were calculated as the average for each mouse (n = 4).



Supplementary Fig. 3: The effects of different schedule on the ratio of cocaine self-administration *in vivo*. The ratio of cocaine self-administration in mice under FR3 was significantly less than that of mice under FR1 ($P < 0.05$).