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Supplementary online material

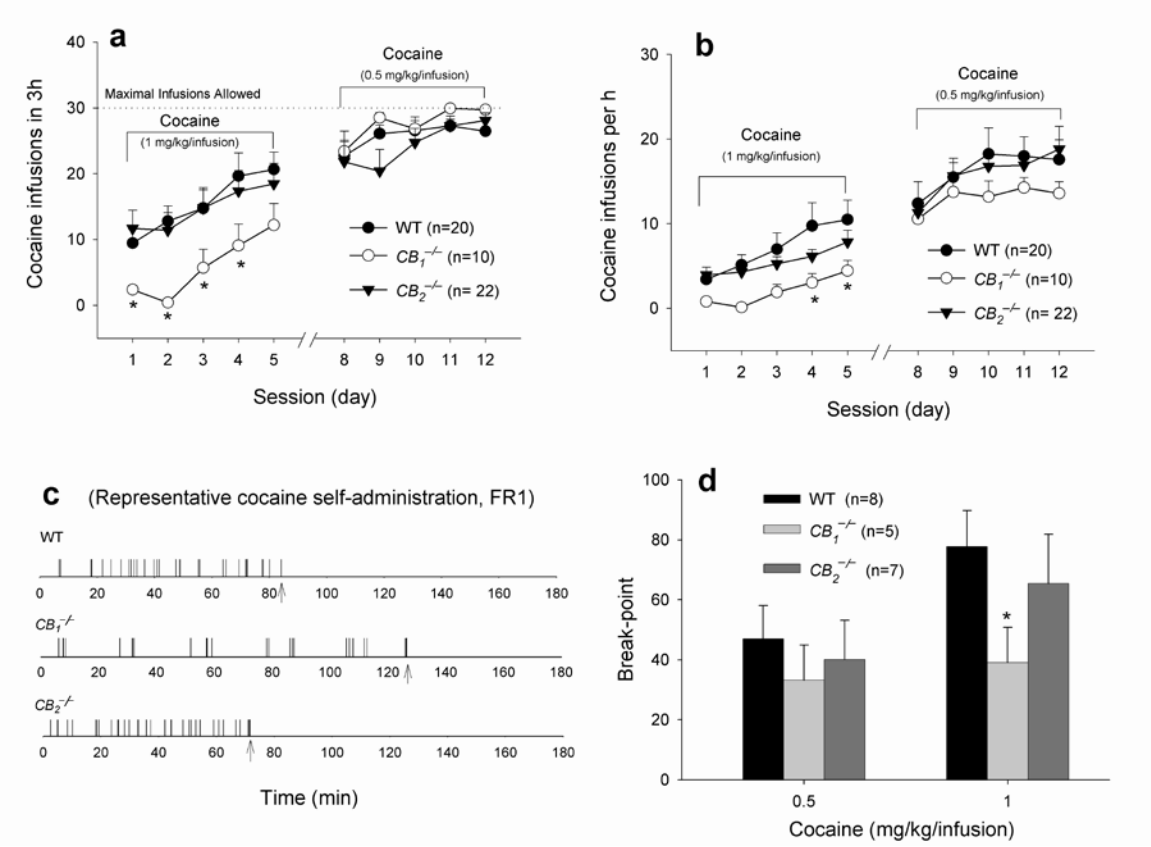
Brain Cannabinoid CB_2 Receptors Modulate Cocaine's Actions in Mice

Zheng-Xiong Xi[1, *], Xiao-Qing Peng[1, †], Xia Li[1, †], Rui Song[1, 2, †], Haiying Zhang[1], Qing-Rong Liu[1], Hong-Ju Yang[1], Guo-Hua Bi[1], Jie Li[1], Eliot L. Gardner[1]

[1]Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD 21224, USA

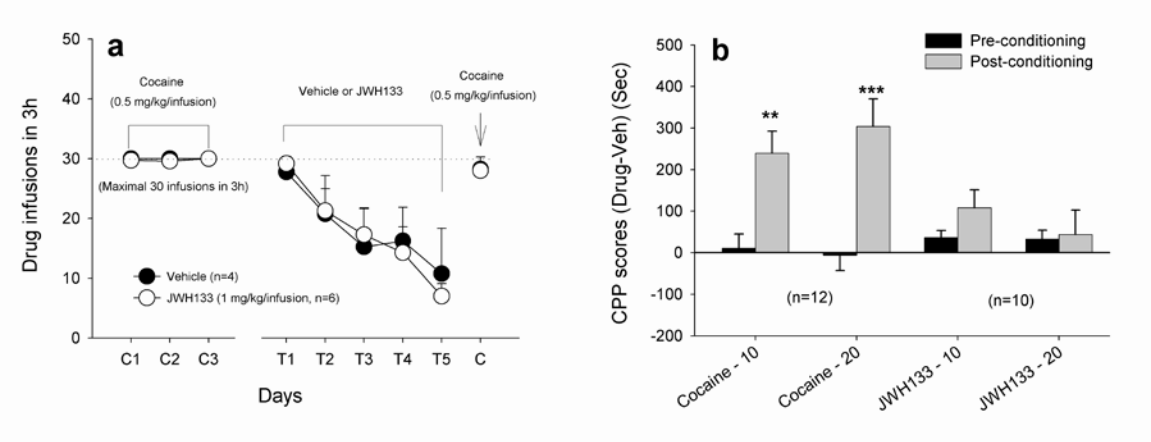
[2]Beijing Institute of Pharmacology and Toxicology, Beijing 100850, China

Supplementary figures:

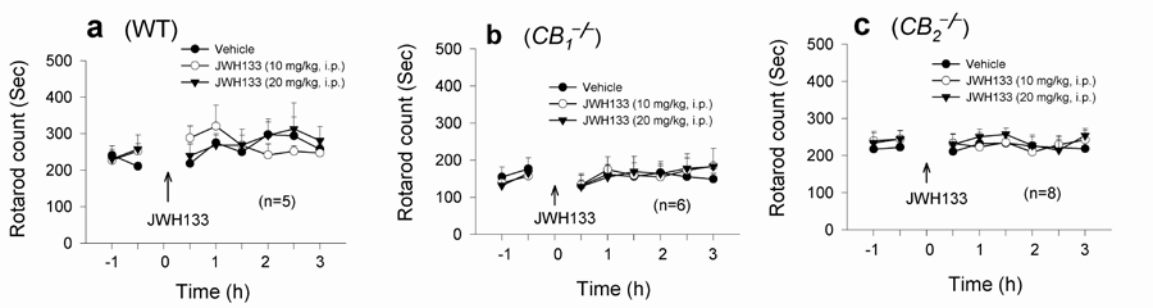


Supplementary Fig. 1 Intravenous cocaine self-administration in WT, $CB_1^{-/-}$ and $CB_2^{-/-}$ mice. **(a)** Time courses of acquisition of intravenous cocaine self-administration during first 10 days of training. $CB_1^{-/-}$, but not $CB_2^{-/-}$, mice displayed a significant reduction in total number of cocaine infusions on days 1-5, compared to WT mice (two-way ANOVA for repeated measures over time, $F_{2,49} = 3.92$, $P < 0.05$). Only data from mice that acquired reliable cocaine self-administration (defined as ≥ 20 infusions during a 3h session) after the first 10 days of training are included. A maximum of 30 infusions per session were allowed to prevent cocaine overdose. **(b)** Mean rates of cocaine self-administration (infusions per h) across animals during first 10 days of cocaine self-administration training. $CB_1^{-/-}$, but not $CB_2^{-/-}$, mice displayed a significant reduction in cocaine self-administration, compared to WT mice ($F_{2,49}= 4.27$, $P < 0.05$). (**c**)

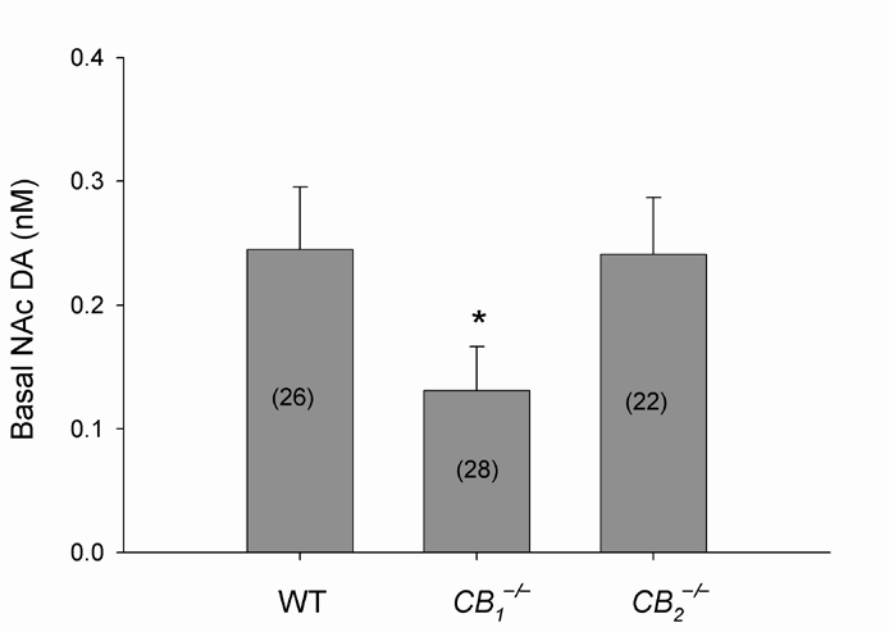
Representative patterns of cocaine self-administration in the three mouse strains. $CB_1^{-/-}$ mice display a distinct "burst-like" pattern of multiple infusions in each drug-taking episode, compared to WT or $CB_2^{-/-}$ mice. (**d**) Break-point levels for cocaine self-administration under PR reinforcement, illustrating a significant reduction in break-point in $CB_1^{-/-}$ mice, compared to WT mice (one-way ANOVA, $F_{1,11}$= 5.48, $P < 0.05$). There was no significant difference in cocaine self-administration behavior between WT and $CB_2^{-/-}$ mice. Arrow (↑) indicates the last of the maximal 30 cocaine infusions. Data are means ± s.e.m. * $P < 0.05$, compared to WT group.



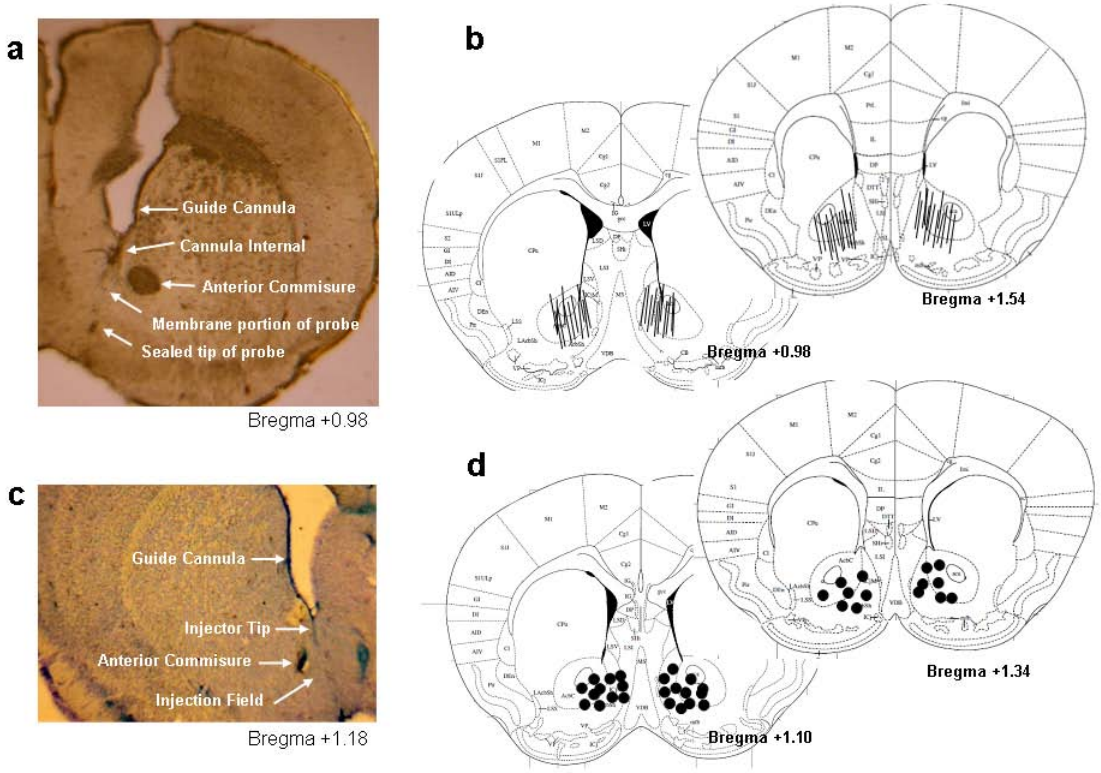
Supplementary Fig. 2 Ability of JWH133 to sustain self-administration or produce conditioned place preference/aversion. (**a**) JWH133 failed to sustain stable self-administration in WT mice previously trained to self-administer cocaine. (**b**) Cocaine (10, 20 mg/kg) produced significant conditioned place preference, while the same doses of JWH133 produced neither conditioned place preference nor conditioned place aversion. Data are means ± s.e.m. C1-C3, the last 3 days of cocaine self-administration. T1-T5, 5 days of JWH133 or vehicle replacement testing. ** P <0.01, *** $P < 0.001$, compared to preconditioning.



Supplementary Fig. 3 Effects of JWH133 on locomotor performance as assessed by rotarod test. JWH133, at the doses that inhibit locomotion and cocaine self-administration, failed to alter rotarod locomotor performance in all three mouse strains.



Supplementary Fig. 4 Basal levels of extracellular DA in the NAc, illustrating a significant reduction in $CB_1^{-/-}$ mice, compared to WT mice. * $P < 0.05$, compared to WT mice. The numbers on the bar figure indicate sample sizes.



Supplementary Fig. 5 Localizations of microdialysis probes and tips of microinjection cannulae in mouse brain. (**a**) Representative microdialysis probe track. (**b**) Schematic reconstructions of positions of microdialysis probes in mouse brain, demonstrating that active microdialysis membranes tended to span the length of the core and shell compartments of the NAc. (**c**) Representative microinjection cannula track. (**d**) Schematic reconstructions of positions of microinjection cannulae in mouse brain, demonstrating that the tips of microinjection cannulae were located in the NAc.