

Supplemental Figures S1-S5

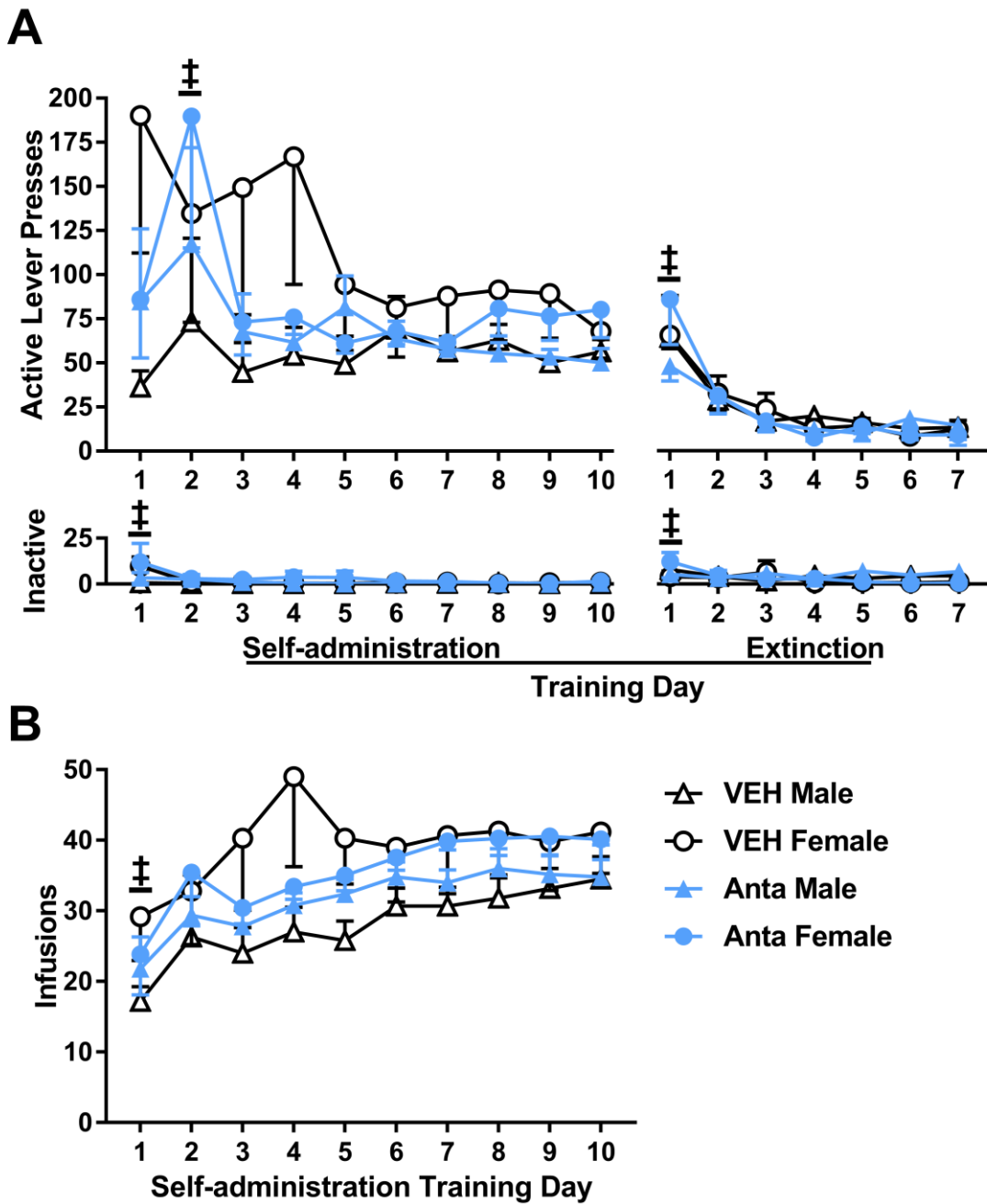


Figure S1. Behavioral history of groups in Experiment 1. (A) Active- and inactive-lever responses (mean/2 h \pm SEM) exhibited by the groups during drug self-administration training (10 sessions) and extinction training (7 sessions). During *cocaine self-administration training*, active-lever responding varied by time, but not sex or subsequent treatment (2 x 2 x 10 ANOVA, time

main effect, $F_{(9,180)} = 3.05$, $p = 0.002$; sex and treatment main and all interaction effects, $F_s \leq 2.40$, $p_s \geq 0.14$). Specifically, active-lever responding decreased after the second session independent of sex or subsequent treatment (\ddagger Tukey's tests, day 2 > days 5-10, $p_s < 0.05$). Similarly, inactive-lever responding decreased after the first cocaine self-administration training session independent of sex or subsequent treatment ($2 \times 2 \times 10$ ANOVA, time main effect only, $F_{(9,180)} = 2.39$, $p = 0.01$, \ddagger Tukey's tests, day 1 > days 6-10, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 2.3$, $p_s \geq 0.15$). During *extinction training*, both active-lever responding ($2 \times 2 \times 7$ ANOVA time main effect only, $F_{(6,120)} = 23.44$, $p < 0.001$, \ddagger Tukey's tests, day 1 > days 2-7, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 1.20$, $p_s \geq 0.32$) and inactive-lever responding ($2 \times 2 \times 7$ ANOVA time main effect only, $F_{(6,120)} = 2.28$, $p = 0.04$, \ddagger Tukey's tests, day 1 > days 4-7, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 1.89$, $p_s \geq 0.09$) decreased after the first session independent of sex or subsequent treatment. **(B)** Cocaine infusions (mean/2 h \pm SEM) obtained by the groups during self-administration training. Cocaine intake increased after the first training session independent of sex or subsequent treatment ($2 \times 2 \times 10$ ANOVA, time main effect only, $F_{(9,180)} = 8.10$, $p < 0.001$, \ddagger Tukey's tests, day 1 < days 2-10, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 3.33$, $p_s \geq 0.80$).

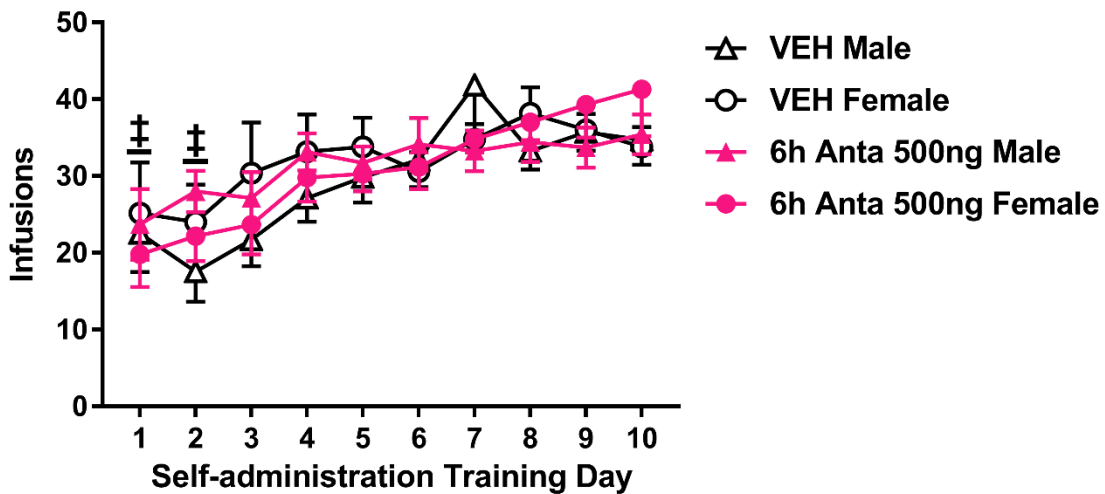
A**B**

Figure S2. Behavioral history of groups in Experiment 2. (A) Active- and inactive-lever responses (mean/2 h \pm SEM) exhibited by the four groups during drug self-administration training (10 sessions) and extinction training (7 sessions). During *cocaine self-administration training*, active-lever responding did not vary as a function of sex, subsequent treatment, or time (2 x 2 x

10 ANOVA, sex, treatment, and time main and all interaction effects, $F_s \leq 1.85$, $p_s \geq 0.06$). Similarly, inactive-lever responding did not vary as a function of sex, subsequent treatment, or time (2 x 2 x 10 ANOVA, all $F_s \leq 1.42$, $p_s \geq 0.25$). During *extinction training*, active-lever responding varied by sex depending on time but not subsequent treatment (2 x 2 x 7 ANOVA, time x sex interaction, $F_{(6,126)} = 2.40$, $p = 0.03$; time main effect, $F_{(6,126)} = 11.08$, $p < 0.001$; sex main and all other interaction effects, $F_s \leq 3.32$, $p_s \geq 0.08$). Females exhibited more active-lever responding than males during the first and second extinction sessions, independent of subsequent treatment ($\$$ Tukey's tests, $p < 0.05$). Furthermore, males exhibited less active-lever responding after the first extinction session (\pm Tukey's tests, day 1 > 2-7), whereas females exhibited less active-lever responding after the second extinction session (\pm Tukey's tests, 1-2 > 3-7, $p < 0.05$). Inactive-lever responding during extinction training decreased after the first session independent of sex or subsequent treatment (2 x 2 x 7 ANOVA, time main effect, $F_{(6,126)} = 4.75$, $p < 0.001$, \pm Tukey's tests, day 1 > days 2-7, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 1.90$, $p_s \geq 0.09$). **(B)** Cocaine infusions (mean/2 h \pm SEM) obtained by the four groups during self-administration training. Cocaine intake increased over time independent of sex or subsequent treatment (2 x 2 x 10 ANOVA, time main effect, $F_{(9,189)} = 13.14$, $p < 0.001$, \pm Tukey's tests, days 1-2 < days 4-10, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 1.64$, $p_s \geq 0.11$).

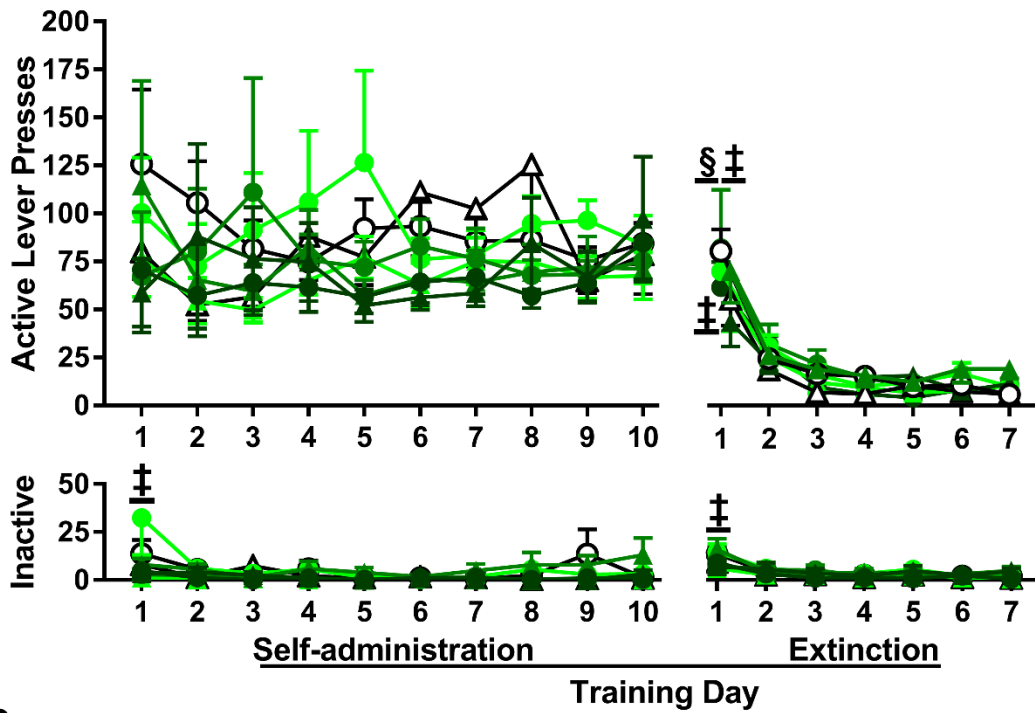
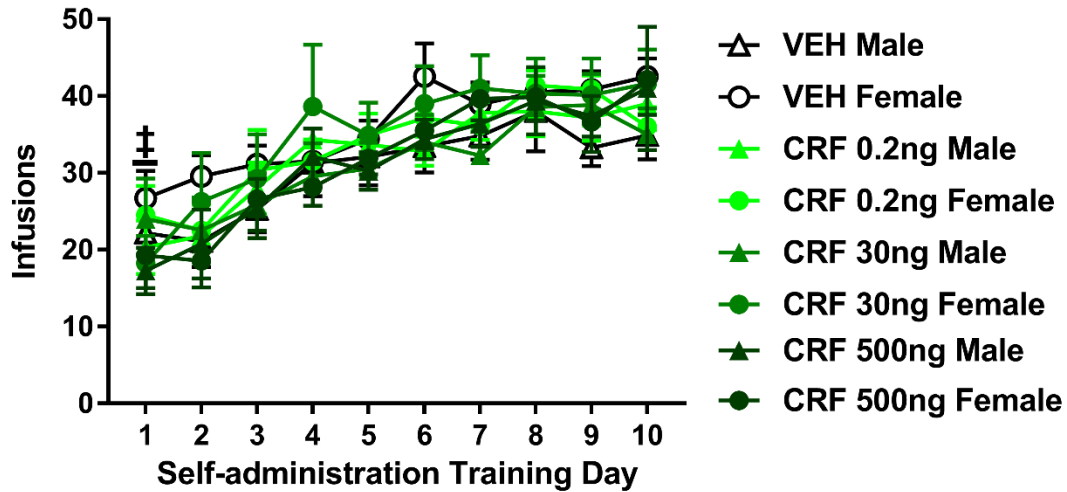
A**B**

Figure S3. Behavioral history of groups in Experiment 3. (A) Active- and inactive-lever responses (mean/2 h \pm SEM) exhibited by the eight groups during drug self-administration training (10 sessions) and extinction training (7 sessions). During *cocaine self-administration training*,

active-lever responding did not vary as a function of sex, subsequent treatment, or time (2 x 4 x 10 ANOVA, sex, treatment, and time main and all interaction effects, $F_s \leq 0.67$, $p_s \geq 0.42$). Inactive-lever responding decreased after the first session, independent of sex or subsequent treatment (2 x 4 x 10 ANOVA, \ddagger time main effect only, $F_{(9,531)} = 3.74$, $p < 0.001$, Tukey's tests, day 1 > days 2-10, $p_s < 0.05$; sex and treatment main and all interaction effects, $F_s \leq 1.58$, $p_s \geq 0.12$). During *extinction training*, active-lever responding varied by sex depending on time but not subsequent treatment (2 x 4 x 7 ANOVA, sex x time interaction effect, $F_{(6,372)} = 2.39$, $p = 0.03$; time main effect, $F_{(6,372)} = 77.41$, $p < 0.001$; treatment main and all other interaction effects, $F_s \leq 0.82$, $p_s \geq 0.37$). Females exhibited more responding than males during the first extinction session, independent of subsequent treatment (\S Tukey's test, $p < 0.05$). Furthermore, both females and males exhibited a decrease in responding after the first extinction session, independent of subsequent treatment (\ddagger Tukey's tests, day 1 > days 2-7, $p_s < 0.05$). Inactive-lever responding during extinction training decreased after the first session independent of sex or subsequent treatment (2 x 4 x 7 ANOVA, time main effect only, $F_{(6,372)} = 27.96$, $p < 0.001$, \ddagger Tukey tests, day 1 > days 2-7, $p_s < 0.05$; all other sex, treatment, and time main and two- and three-way interaction effects, $F_s \leq 1.46$, $p_s \geq 0.10$). (B) Cocaine infusions (mean/2 h \pm SEM) obtained by the eight groups during self-administration training. Cocaine intake increased after the first training session independent of sex or subsequent treatment (2 x 4 x 10 ANOVA, time main effect, $F_{(9,531)} = 48.32$, $p < 0.001$, \ddagger Tukey's tests, day 1 < days 3-10, $p_s < 0.05$; sex and treatment main effect and all interaction effects, $F_s \leq 2.13$, $p_s \geq 0.15$).

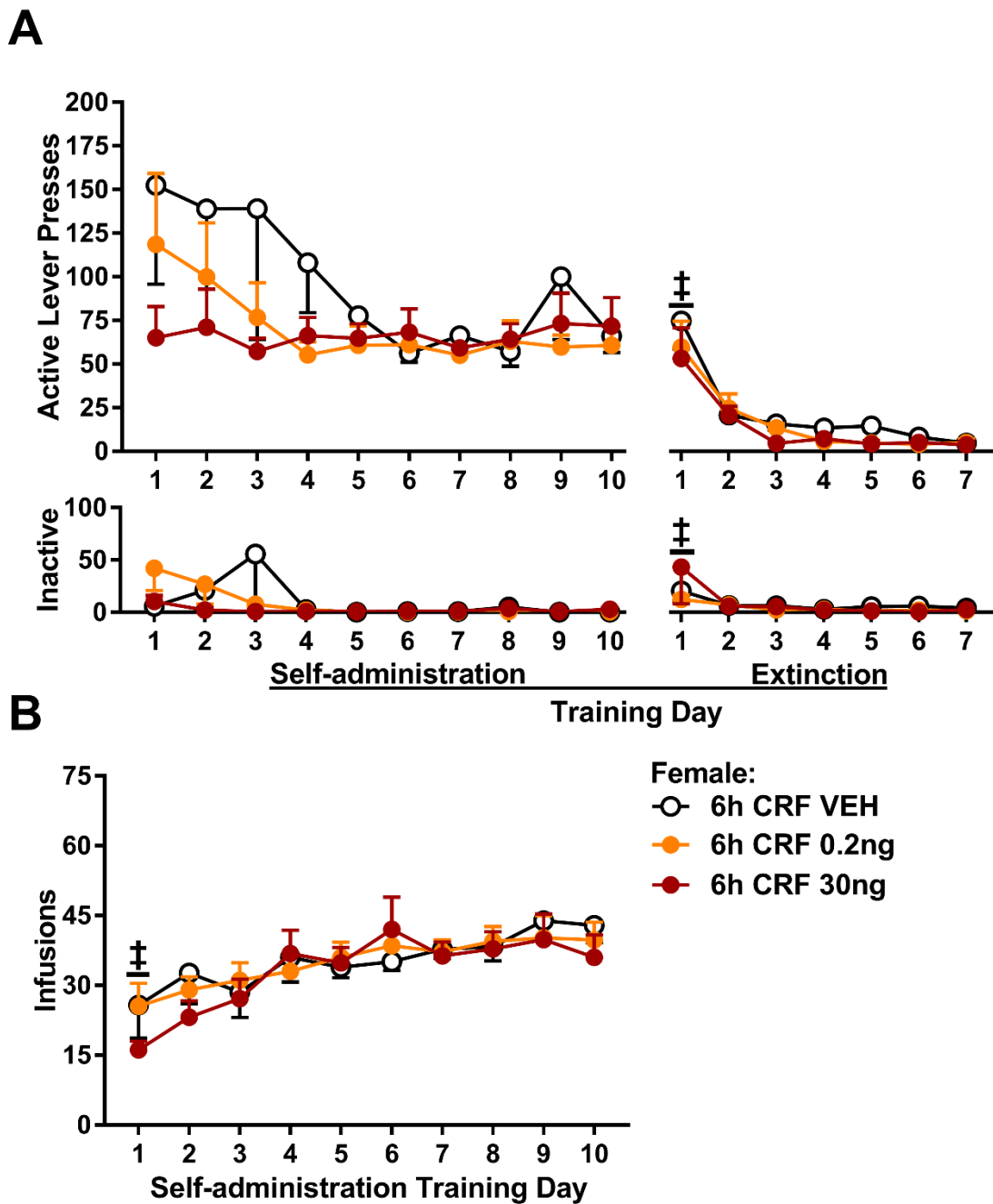


Figure S4. Behavioral history of groups in Experiment 4. (A) Active- and inactive-lever responses (mean/2 h \pm SEM) exhibited by the three groups during drug self-administration training (10 sessions) and extinction training (7 sessions). **Since treatment effects in Experiment 3 were observed in female subjects only, males were not included in this control experiment.**

During *cocaine self-administration training*, neither active-lever responding (3 x 10 ANOVA, treatment and time main and interaction effects, $F_s \leq 1.69$, $p_s \geq 0.21$) nor inactive-lever responding varied as a function of subsequent treatment or time (3 x 10 ANOVA, treatment and time main and interaction effects, $F_s \leq 1.37$, $p_s \geq 0.20$). During *extinction training*, both active-lever responding (3 x 7 ANOVA, time main effect only, $F_{(6,126)} = 30.2$, $p < 0.001$, \ddagger Tukey's tests, session 1 > sessions 2-7, $p_s < 0.05$; treatment main and interaction effects, $F_s \leq 1.22$, $p_s \geq 0.32$) and inactive-lever responding (3 x 7 ANOVA, time main effect, $F_{(6,126)} = 5.22$, $p < 0.001$, \ddagger Tukey's tests, day 1 > days 2-7, $p_s < 0.05$; treatment main and interaction effects, $F_s \leq 0.89$, $p_s \geq 0.56$) decreased after the first extinction session independent of subsequent treatment. **(B)** Cocaine infusions (mean/2 h \pm SEM) obtained by the three groups during self-administration training. Cocaine intake increased after the first session independent of subsequent treatment (3 x 10 ANOVA, time main effect only, $F_{(9,180)} = 10.68$, $p < 0.001$, \ddagger Tukey's tests, day 1 < days 4-10, $p_s < 0.05$; treatment main and interaction effects, $F_s \leq 0.19$, $p_s \geq 0.83$).

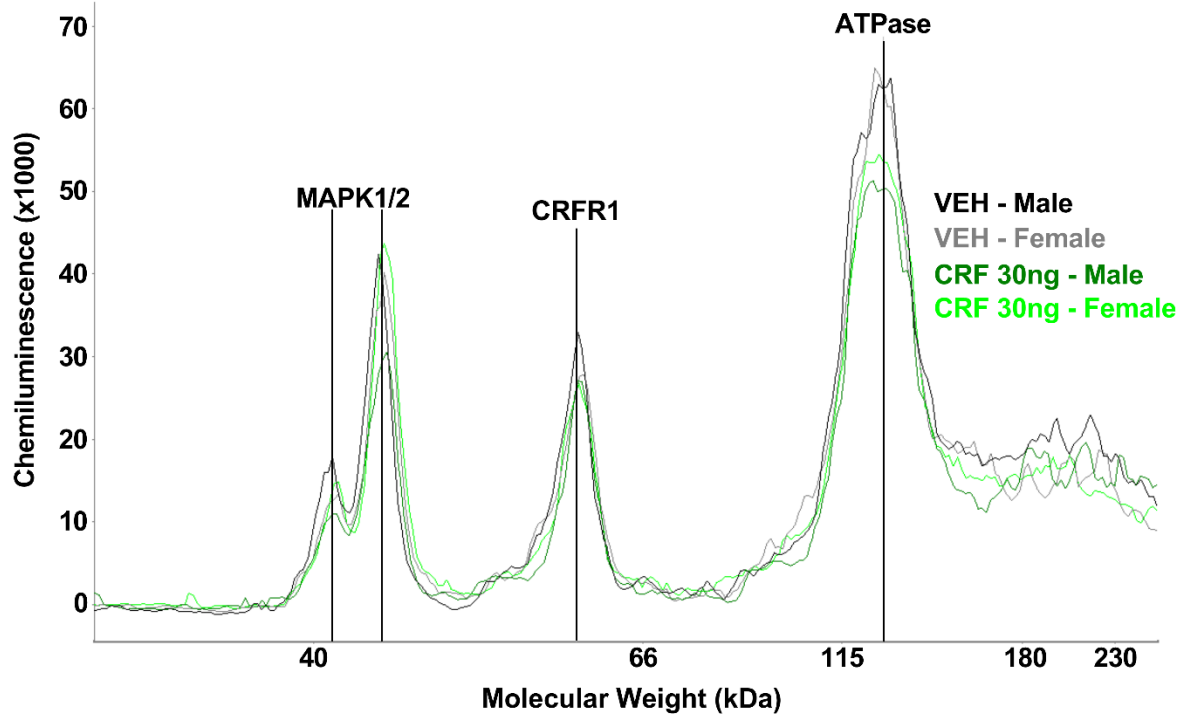
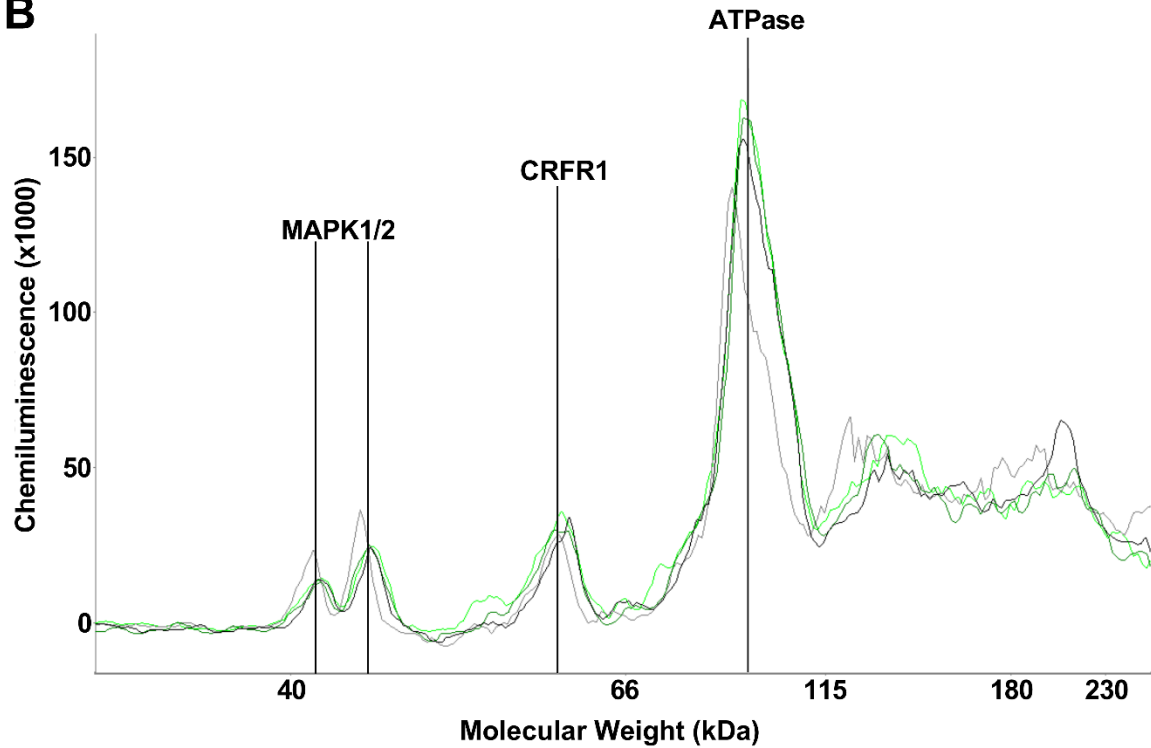
A**B**

Figure S5. Intra-BLA CRF treatment does not alter total or biotinylated (cell surface) CRFR1 levels. Male and female rats received bilateral vehicle or CRF (30 ng/0.5 μ l/hemisphere) infusions into the BLA. BLA tissue was collected 30 minutes later. Total and biotinylated CRFR1, MAP1/2 (indicator of BLA cell integrity), and ATPase (loading control) levels were detected using an automated capillary electrophoresis immunoassay on the Wes ProteinSimple instrument. The area under the curve for CRFR1 was normalized to the area under the curve for loading control. **(A)** Representative electropherograms for total protein fractions obtained from one subject per group. **(B)** Representative electropherograms for biotinylated protein fractions obtained from one subject per group.