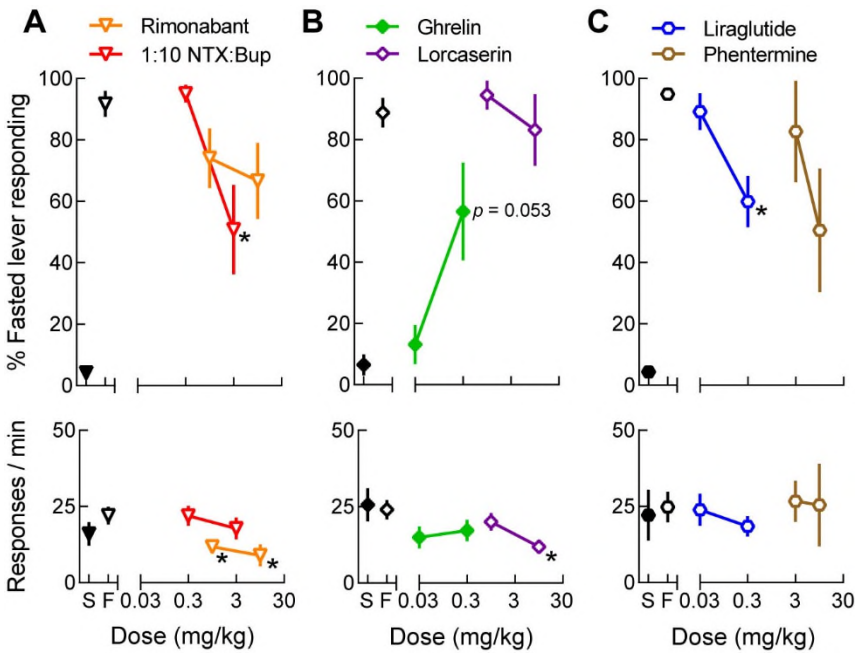


**Figure S1. Effects of orexigenic and anorexigenic compounds on interoceptive hunger and satiety cues. Related to Figure 2.**

**(A)** *Left segment;* 'S': sated mice pretreated with saline; 'F' fasted mice pretreated with saline. *Right segment;* the anorexigenic cannabinoid receptor 1 antagonist rimonabant in fasted mice did not significantly alter fasted-associated lever responding ($F(1.68, 8.39) = 2.81$, $p = 0.12$) but did decrease response rate ($F(1.94, 9.67) = 10.31$, $p = 0.0042$; Dunnett's post-tests: F vs. 1 mg/kg, $^*p = 0.026$, F vs. 10 mg/kg, $^*p = 0.018$). The anorexigenic combination of the μ-opioid receptor antagonist naltrexone (NTX) and the dopamine-norepinephrine reuptake inhibitor bupropion (BUP) (1 NTX: 10 BUP ratio, data plotted by BUP dose) in fasted mice decreased fasted-associated lever responding ($F(1.07, 5.33) = 10.45$, $p = 0.020$; Dunnett's post-test: F vs. 3:30 mg/kg, $^*p = 0.026$) but did not significantly affect response rate ($F(1.30, 6.52) = 1.45$, $p = 0.29$). $n = 6$ mice per group for all tests.

**(B)** *Left segment;* 'S': sated mice pretreated with saline; 'F' fasted mice pretreated with saline. *Right segment;* the orexigenic hormone ghrelin in sated mice significantly increased fasted-associated lever responding ($F(1.13, 5.65) = 8.74$, $p = 0.026$; Dunnett's post-test: S vs. 1 mg/kg, $p = 0.053$) but did not affect response rate ($F(1.06, 5.30) = 0.11$, $p = 0.763$). The anorexigenic 5-$HT_{2C}$ receptor agonist lorcaserin in fasted mice did not decrease fasted-associated lever responding ($F(1.28, 6.41) = 1.14$, $p = 0.35$) but did significantly decrease response rate ($F(1.64,$

8.18) = 9.00, $p$ = 0.011; Dunnett's post-test: F vs. 10 mg/kg, *$p$ = 0.020). $n$ = 6 mice per group for all tests.

**(C)** *Left segment;* 'S': sated mice pretreated with saline; 'F' fasted mice pretreated with saline. *Right segment;* the anorexigenic glucagon-like peptide-1 receptor agonist liraglutide in fasted mice significantly decreased fasted-associated lever responding ($F$(1.93, 9.63) = 13.83, $p$ = 0.0016; Dunnett's post-test: F vs. 0.3 mg/kg, *$p$ = 0.011) but did not affect response rate ($F$(1.89, 9.47) = 0.99, $p$ = 0.40). The amphetamine-like anorexigenic phentermine in fasted mice did not affect fasted-associated lever responding ($F$(1.80, 9.01) = 3.29, $p$ = 0.088) or response rate ($F$(1.21, 6.05) = 0.021, $p$ = 0.92). $n$ = 6 mice per group for all tests.

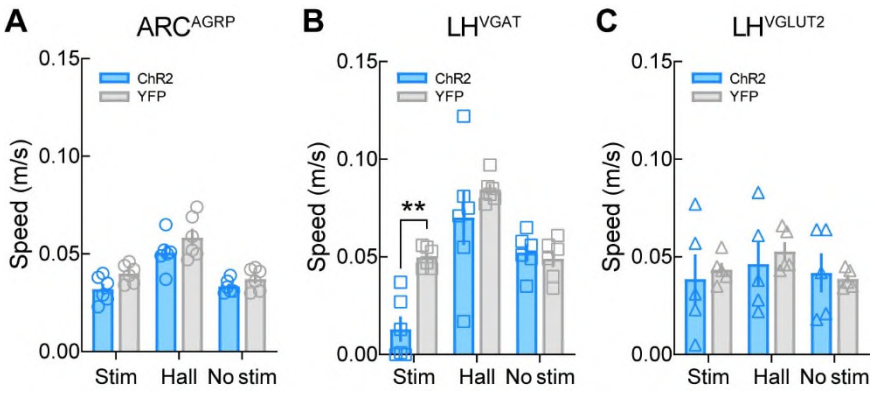


**Figure S2. Real-time place preference effects of ARC$^{AGRP}$, LH$^{VGAT}$, and LH$^{VGLUT2}$ neuronal activation. Related to Figure 3.**

**(A)** ARC$^{AGRP}$ activation had no effect on average speed (*n* = 6 mice per group; $F(2, 20) = 0.83$, $p = 0.45$).

**(B)** LH$^{VGAT}$ activation significantly decreased average speed (*n* = 6 mice per group; $F(2, 20) = 4.91$, $p = 0.018$; Bonferroni's post-test: $^{**}p = 0.0021$).

**(C)** LH$^{VGLUT2}$ activation had no effect on average speed (*n* = 5 mice per group; $F(2, 16) = 0.36$, $p = 0.70$).

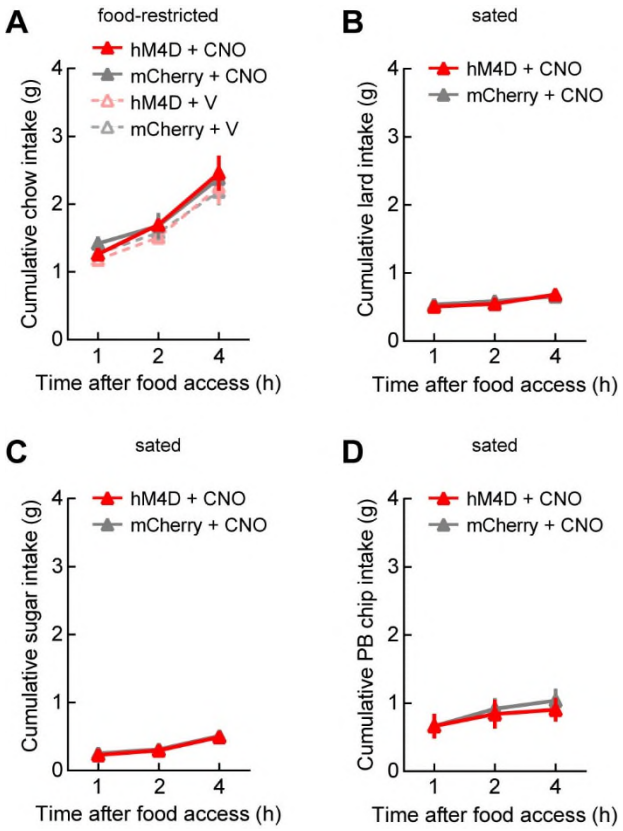


**Figure S3. LH$^{VGLUT2}$ inhibition did not alter caloric food intake. Related to Figure 3.**

**(A)** No changes in standard chow intake (three-way mixed-model ANOVA only revealed a significant main effect of time, $F(2, 16) = 111.0$, $p < 0.0001$). $n = 5$ mice per group.

**(B)** No changes in lard intake (two-way repeated-measures ANOVA group × time interaction: $F(2, 16) = 0.48$, $p = 0.63$). $n = 5$ mice per group.

**(C)** No changes in sucrose intake ($F(2, 16) = 0.020$, $p = 0.98$). $n = 5$ mice per group.

**(D)** No changes in peanut butter chip intake ($F(2, 16) = 0.30$, $p = 0.74$). $n = 5$ mice per group.

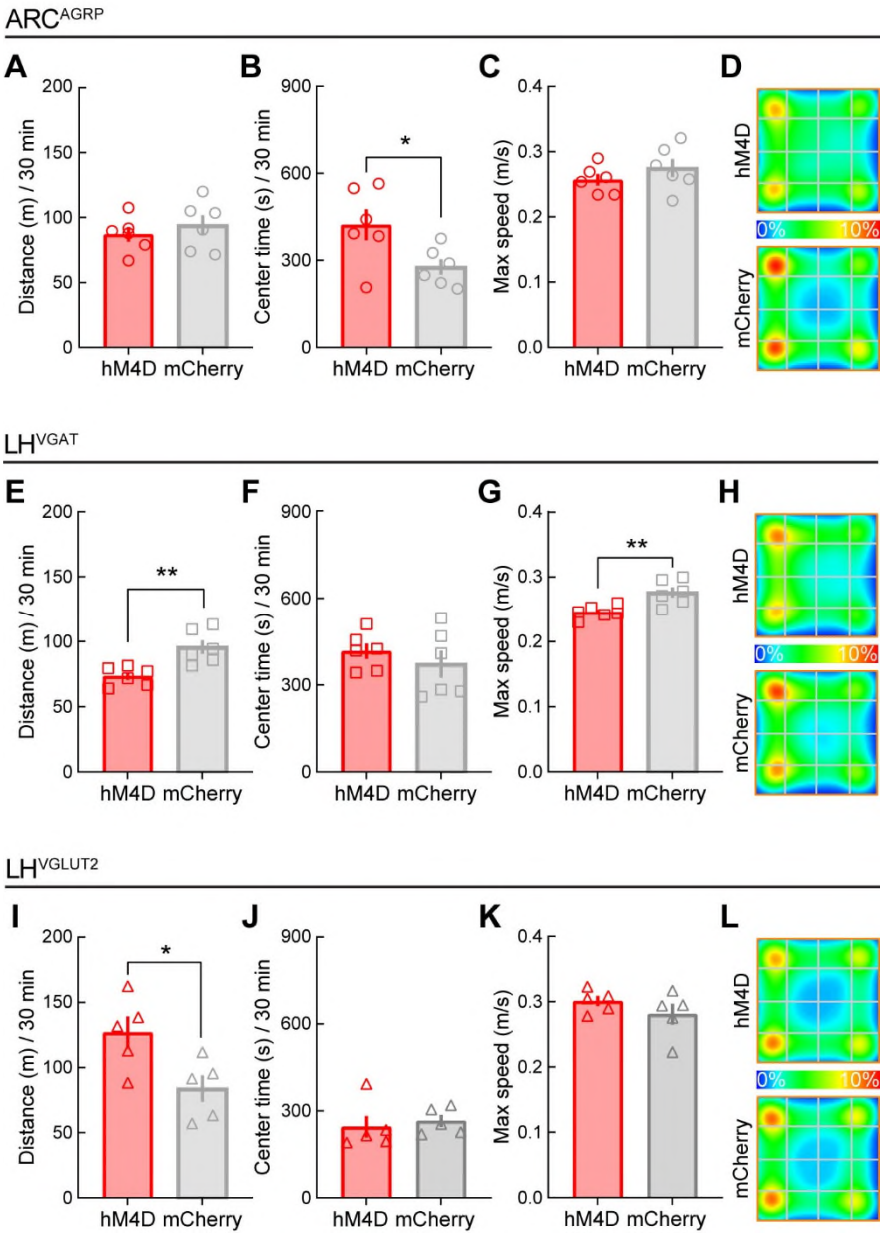


**Figure S4. Effects of ARC$^{AGRP}$, LH$^{VGAT}$, and LH$^{VGLUT2}$ inhibition in the open field test. Related to Figure 3.**

**(A)** ARC$^{AGRP}$ inhibition did not affect total distance ($t(10) = 0.74$, $p = 0.48$), **(B)** did increase center zone time ($t(10) = 2.43$, $^*p = 0.035$), and **(C)** did not affect maximum speed ($t(10) = 1.09$, $p = 0.30$). $n = 6$ mice per group.

**(D)** $ARC^{AGRP}$ group average location open field heat maps (*n* = 6 mice per group). Scale is percentage of time spent in location.

**(E)** $LH^{VGAT}$ inhibition decreased total distance ($t(10) = 3.70$, $^{**}p = 0.0041$), **(F)** did not affect center zone time ($t(10) = 0.84$, $p = 0.42$), and **(G)** decreased maximum speed ($t(10) = 3.39$, $^{**}p = 0.0069$). *n* = 6 mice per group.

**(H)** $LH^{VGAT}$ group average location open field heat maps (*n* = 6 for each group). Scale is percentage of time spent in location.

**(I)** $LH^{VGLUT2}$ inhibition increased total distance ($t(8) = 2.67$, $^{*}p = 0.029$) but did not affect **(J)** center zone time ($t(8) = 0.46$, $p = 0.66$) or **(K)** maximum speed ($t(8) = 1.14$, $p = 0.29$). *n* = 5 mice per group.

**(L)** $LH^{VGLUT2}$ group average location open field heat maps (*n* = 5 mice per group). Scale is percentage of time spent in location.