Effects of Cannabinoid and Opioid Derivatives on ARC^{AgRP} → PVN Synaptic Connection in AgRP Transgenic Mice

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INTRODUCTION &AIM

Neurons secreting agouti-related protein (AgRP) are localized in the hypothalamus arcuate (ARC) nucleus and play an important role in food intake and energy expenditure. Manipulation of these neurons causes alteration in food intake. In addition, AgRP neurons play a key role in appetite regulation by sending intense axonal projection to the paraventricular nucleus (PVN). Neuromodulators that influence the strength of this link are also likely to be critical in regulating the appetite mechanism. For this purpose, the effects of cannabinoids, opioids and other appetite-regulating neuromodulators on the synaptic properties of the ARC^{AgRP} → PVN connection were investigated in our study.

METHODS

Forty (6-8 weeks old) transgenic AgRP-Ires-cre (Jax. Lab. #012899) mice were used.

Ex-vivo (29 mice)

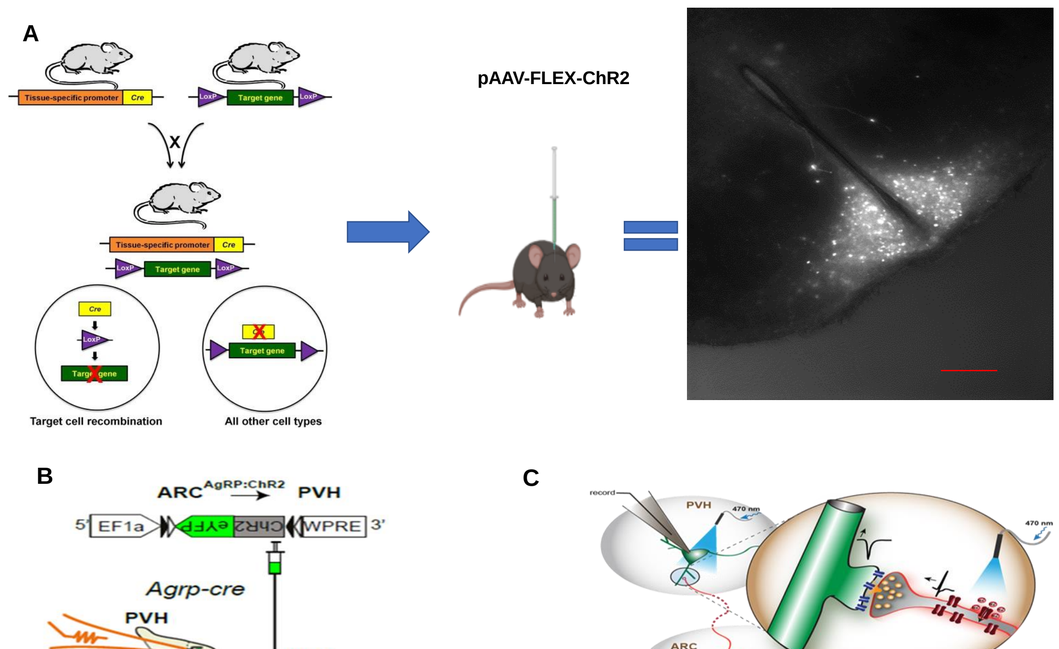


Figure 1. ArcAgRP->PVH synaptic connectivity features A) Using the Cre technique and injected virüs B) Image of ChR2 injection into the hypothalamus arcuate region C) Optogenetic stimulation of AgRP neuron axons during recording from neurons from the PVH region D) All projection map of AgRP-Cre mouse injected with GFP E) AgRP-Cre injected with ChR2

RESULTS

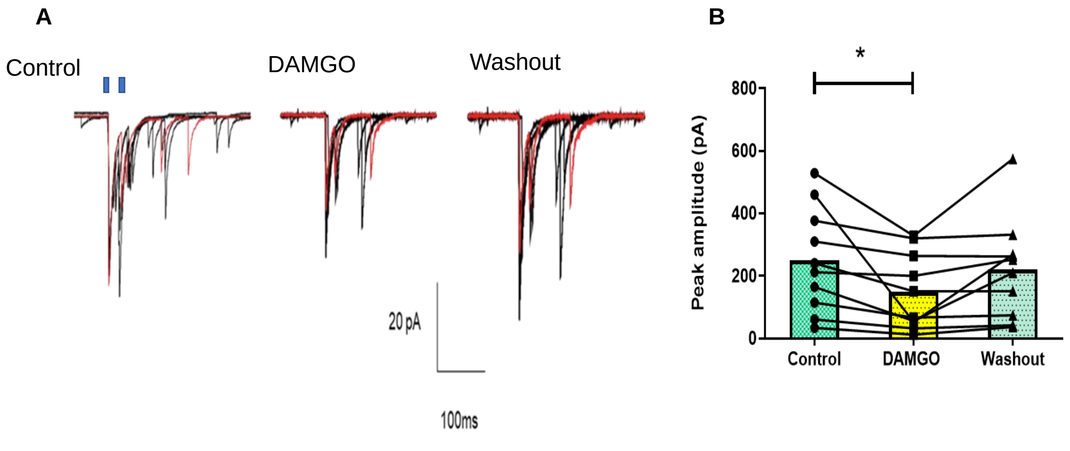
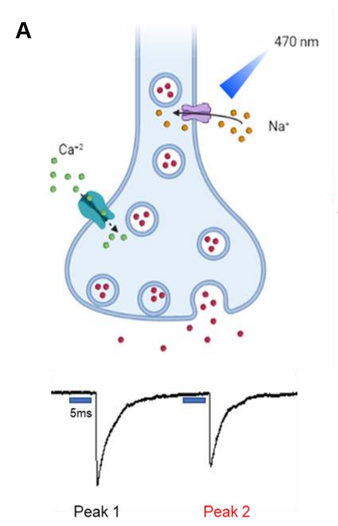


Figure 2. A) Peak amplitude recording from the Arc^{AgRP}→^{PVH} projection. B) The peak amplitude plot of DAMGO in PVH neurons after stimulation of AgPR neuron axons (Control: 250.4 ±52.81 pA, DAMGO: 148.3±38.6 pA, Naloxone: 220.5±51.11 pA n= 10 neurons / 4 mice) (one-way ANOVA, P< 0.05, Tukey's multiple comparisons test)



$$\frac{Peak\ 2}{Peak\ 1} = PPR$$

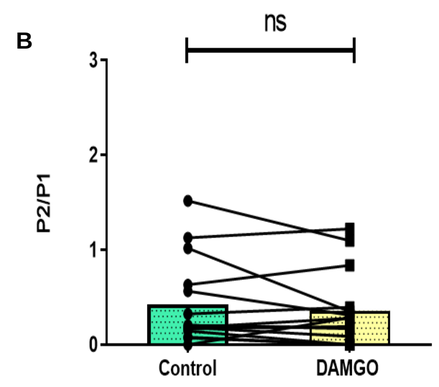


Figure 3. A-B) Release probability plot of synaptic outputs from AgRP neurons (Control: 0.42 ±0.11, DAMGO: 0.36±0.09, n= 15 neurons / 4 mice) (T-test nonparametric Wilcoxon matched-pairs signed rank P=0.45)

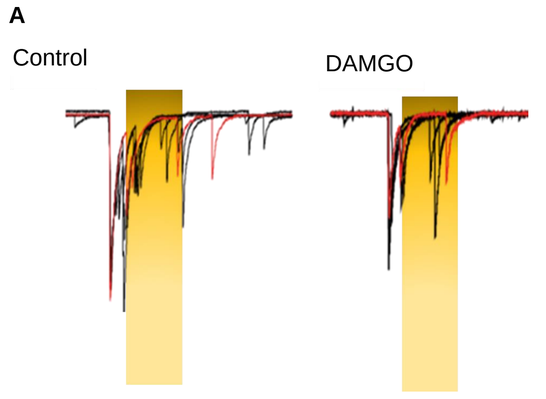
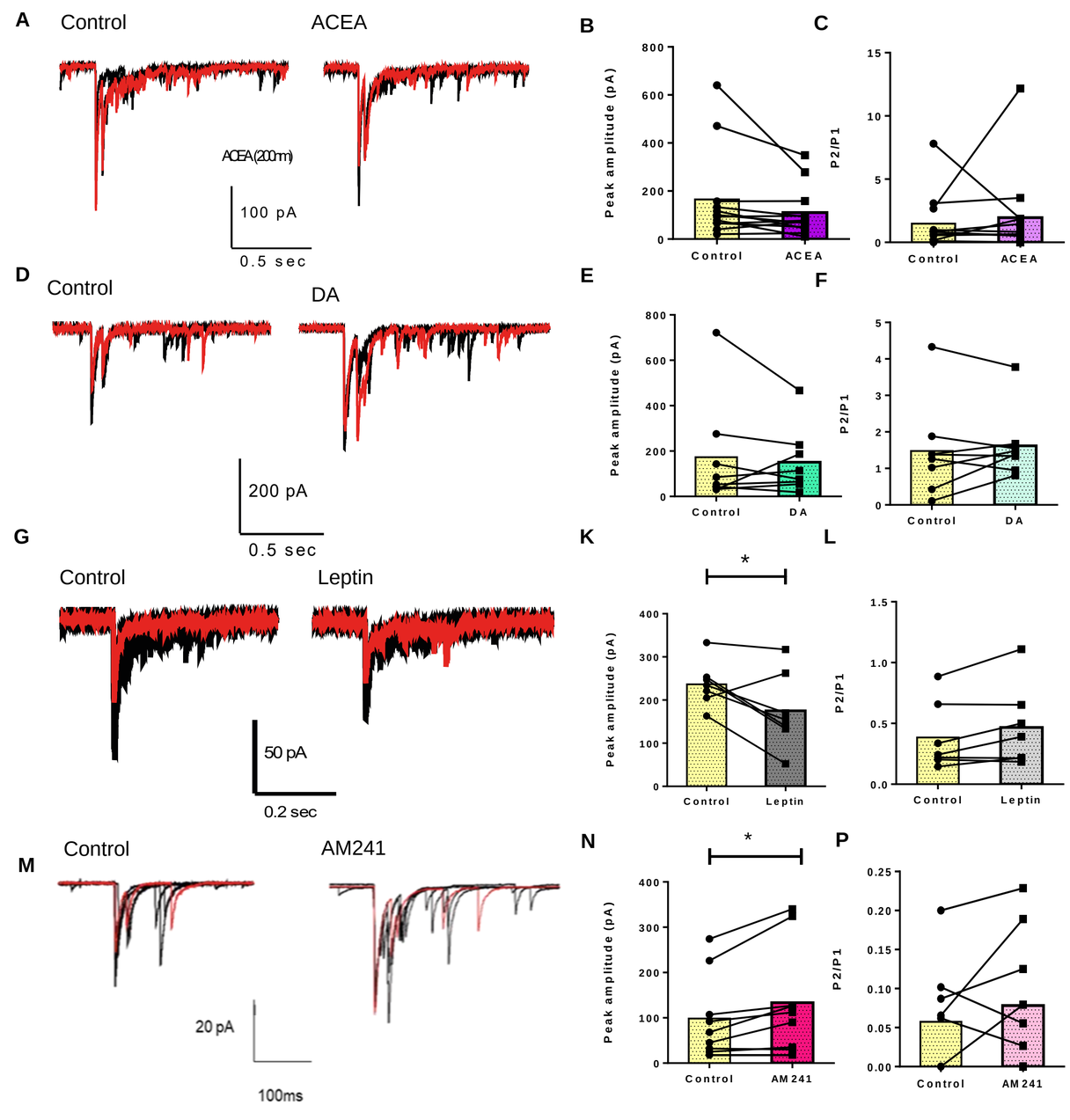


Figure 4. A,B,C) Frequency and area graph after stimulation of AgRP neuron axons in post-synaptic neurons (Control: 8.97±0.92 Hz n=15 neurons, DAMGO: 5.37±0.92 Hz n=15 neurons / 4 mice) , (Control: 11827.30±3580.14ms.pA n=15 neurons, DAMGO: 5857.75 ±2053.75 ms.pA n=15 neurons / 4 mice) (T-test nonparametric Wilcoxon matched pairs signed rank P<0.0001, P= 0.0054).



CONCLUSION

In this study, the effects of cannabinoid and opioid derivatives on the axonal terminals of AgRP neurons were investigated for the first time. Our results show that opioids and leptin hormone have strong modulatory effects on ARC^{AgRP} → PVN synaptic connection. Cannabinoids and dopamine did not affect this neural circuit which has an important role in food intake.