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Neuromodulatory regulation of synaptic transmission in the ARC AgRP→PVN circuit revealed by optogenetics

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MAIN POINTS

- Optogenetic and electrophysiological recordings revealed functional synaptic connectivity in the ARC AgRP→PVN pathway.
- Activation of leptin and kappa-opioid receptors significantly reduced synaptic transmission in this circuit.
- Dopamine and MTII did not significantly affect synaptic strength; presynaptic release probability remained unchanged.

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ABSTRACT

Aim: To investigate how dopamine, leptin, kappa opioid receptor signaling, and melanocortin receptors modulate synaptic transmission in the ARC AgRP→PVN pathway.

Materials and Methods: We combined optogenetic stimulation with whole-cell electrophysiological recordings to directly assess synaptic strength and connectivity. ARC AgRP neurons were selectively activated via AAV-FLEX-ChR2-mediated expression of channelrhodopsin, and postsynaptic responses were recorded from PVN neurons. The effects of dopamine, leptin, kappa opioid, and MTII on synaptic transmission were evaluated, allowing precise analysis of modulatory influences on this hypothalamic feeding circuit.

Results: Leptin and a kappa opioid receptor agonist significantly reduced the synaptic strength of the ARC AgRP→PVN pathway, as reflected by a decrease in the peak amplitude of optogenetically evoked synaptic responses in PVN neurons. In contrast, neither dopamine nor MTII produced significant changes in synaptic strength or neurotransmitter release at this connection ($p>0.05$).

Conclusion: These findings demonstrate that leptin and kappa-opioid receptor activation suppress synaptic transmission in the ARC AgRP→PVN circuit, whereas dopamine and melanocortin receptor activation by MTII have minimal effects on this pathway. Collectively, these results provide new insights into the neuromodulatory mechanisms regulating hypothalamic feeding circuits and highlight potential targets for interventions aimed at controlling appetite and energy balance.

Keywords: AgRP neurons, Synaptic transmission, Dopamine, Leptin, Opioid receptor, Electrophysiology

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INTRODUCTION

Agouti-related peptide (AgRP) neurons located in the arcuate nucleus (ARC) of the hypothalamus play a central role in the regulation of feeding behavior and whole-body energy homeostasis. These neurons are strongly activated during energy deficit and promote food intake and weight gain through their widespread projections to multiple hypothalamic and extra-hypothalamic regions [1,2]. Among these projection targets, the paraventricular nucleus (PVN) of the hypothalamus is considered one of the most critical nodes in the neural circuitry controlling appetite, neuroendocrine signaling, and autonomic regulation [3]. Functional studies have demonstrated that the ARC AgRP→PVN pathway represents a key circuit that rapidly drives feeding behavior when AgRP neurons are activated [1,4].

AgRP neurons exert their effects through the release of several neurotransmitters and neuropeptides, including γ-aminobutyric acid (GABA), neuropeptide Y (NPY), and AgRP itself. NPY is a potent orexigenic peptide that stimulates feeding through activation of Y receptors in downstream hypothalamic targets such as the PVN [2]. In addition, AgRP functions as an endogenous antagonist of melanocortin receptors, particularly melanocortin-4 receptors (MC4R), which are abundantly expressed in PVN neurons and are well known to regulate appetite and energy expenditure [5,6]. Pharmacological activation of melanocortin signaling using agonists such as melanotan-II (MTII) has been shown to suppress food intake and modulate hypotha-

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lamic neuronal activity, highlighting the importance of the melanocortin system in feeding regulation [7].

Beyond classical neuropeptide signaling, feeding circuits are also modulated by several neuromodulatory systems. Dopamine signaling has been implicated in motivational and reward-related aspects of feeding behavior and may influence hypothalamic circuits involved in energy balance [8,9]. Leptin, an adipocyte-derived hormone, provides a key hormonal signal of energy status and acts directly on hypothalamic neurons, including AgRP neurons, to suppress feeding and regulate energy expenditure [10,11]. In addition to these signals, opioid systems have emerged as important modulators of feeding behavior. In particular, activation of kappa opioid receptors (KOR) has been shown to influence appetite, stress responses, and reward processing, suggesting that KOR signaling may interact with hypothalamic circuits that regulate energy homeostasis [12,13].

Recent advances in optogenetics and electrophysiological techniques have enabled precise investigation of functional connectivity within hypothalamic circuits. Several studies have used these approaches to examine how neuromodulators influence synaptic transmission between AgRP neurons and their downstream targets [1,14]. Despite extensive evidence that dopamine, leptin, melanocortin signaling, and opioid systems influence feeding behavior, the direct effects of these neuromodulators on synaptic transmission within the ARC AgRP→PVN pathway remain poorly understood.

Therefore, in the present study we investigated how dopamine, leptin, a kappa opioid receptor agonist, and the melanocortin receptor agonist MTII modulate synaptic transmission between ARC AgRP neurons and PVN neurons. Using a combination of optogenetic stimulation and whole-cell electrophysiological recordings, we aimed to directly characterize the modulatory effects of these signaling pathways on the ARC AgRP→PVN synaptic connection.

MATERIALS AND METHODS

Mice

A total of twenty AgRP-Cre male mice (4–6 weeks old; stock number 012899; Jackson Laboratories, ME, USA) were included in the experiments. Animals were maintained under controlled conditions (21 ± 1 °C) with ad libitum access to standard chow and water. The AgRP-Cre line expressing Cre recombinase [15] was maintained through homozygous × homozygous backcrossing. Mouse breeding was performed at the Experimental Research Center of the Yeditepe University Faculty of Medicine (YUDETAM) in Istanbul, Türkiye. The Yeditepe University Animal Experiments Ethics Committee approved all experimental protocols (Decision No: 2023/11-06, Date: 09.11.2023).

Stereotaxic surgical procedures

Intracranial injections were carried out as previously described [16]. Briefly, mice aged P50–P60 were anesthetized with isoflurane and secured in a stereotaxic frame (David Kopf Inst, CA, USA). After a small scalp incision was made, the skull was exposed and drilled to form an injection site. Bilateral injections of 250–500 nL pAAV-FLEX-ChR2 virus were performed in the ARC using a pulled glass pipette (50 μm tip; Drummond PA, USA) [15] at a rate of 60 nL/min. Stereotaxic coordinates relative to bregma were: anterior–posterior (AP) −1.30 mm, dorsal–ventral (DV) −5.75 mm, and lateral ±0.35 mm. Injections were carried out using a micromanipulator (Narishige, NY, USA), taking approximately 30 minutes per site. After pipette withdrawal, the incision was sutured. Mice were allowed 1-2 weeks for recovery and for sufficient ChR2 virus expression before subsequent experiments.

Combined electrophysiology and optogenetic manipulation

Brain slice preparation was conducted as previously described [17]. Briefly, mice were euthanized and their brains were swiftly transferred into an N-methyl-D-glucamine (NMDG)–HEPES–based cutting solution consisting of artificial cerebrospinal fluid (aCSF; in mM: 92 NMDG, 2.5 KCl, 1.25 NaH_2PO_4, 30 $NaHCO_3$, 20 HEPES, 25 glucose, 2 thiourea, 5 Na-ascorbate, 3 Na-pyruvate, 0.5 $CaCl_2{\cdot}2H_2O$, and 10 $MgSO_4{\cdot}7H_2O$). Brain tissue was maintained in ice-cold carbogenated solution (5% CO_2/95% O_2), and 275 μm coronal slices containing the hypothalamus were prepared using a vibratome. Slices were subsequently transferred into HEPES-based incubation aCSF (in mM: 92 NaCl, 30 $NaHCO_3$, 25 glucose, 2.5 KCl, 1.25 NaH_2PO_4, 3 Na-pyruvate, 20 HEPES, 2 $MgSO_4{\cdot}7H_2O$, 2 $CaCl_2{\cdot}2H_2O$, 2 thiourea, 5 Na-ascorbate), which was continuously bubbled with 95% O_2/5% CO_2, and the slices were incubated for at least 1-2 h. Following recovery, slices were transferred to a recording chamber and perfused with standard recording aCSF (in mM: 124 NaCl, 12.5 glucose, 2.5 KCl, 1.25 NaH_2PO_4, 5 HEPES, 24 $NaHCO_3$, 2 $MgSO_4{\cdot}7H_2O$, and 2 $CaCl_2{\cdot}2H_2O$). Whole-cell recordings were performed on PVN neurons using electrodes with tip resistances of 5–6 MΩ. Blue light (470 nm) delivered by a CoolLED system was used to identify synaptic connections. PVN neurons were randomly sampled in AgRP-Cre mice, and upon confirmation of $ARC^{AgRP→PVN}$ synaptic connectivity, a 6–12 min baseline was recorded before applying pharmacological agents (Leptin, 100 nM; dopamine, 50 μM; ACEA, 200 nM; AM241, 200 nM) to the bath solution. The internal recording solution (in mM) consisted of 125 CsCl, 10 HEPES, 5 NaCl, 4 Mg-ATP, 0.6 EGTA, 0.3 Na_2GTP, and 10 QX-314, adjusted to pH 7.30 and 290-300 mOsm. Signals were recorded and analyzed using a MultiClamp 700B amplifier coupled with pCLAMP 11.3 software (Molecular Devices, San Jose, CA) [18].

Imaging

Deeply anesthetized mice were transcardially perfused with 4% paraformaldehyde (PFA) in 0.1 M phosphate buffer

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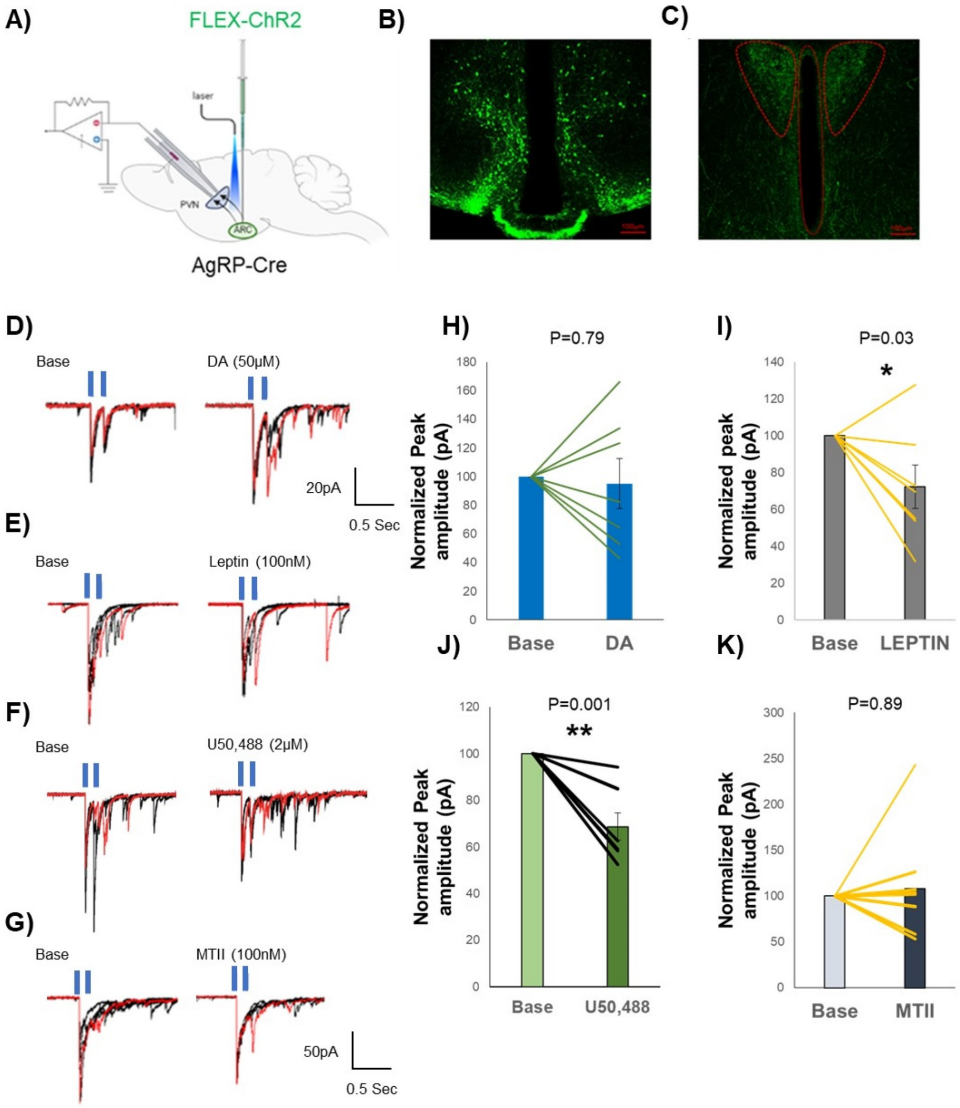

Figure 1. Pharmacological modulation of ARC AgRP→PVN synaptic transmission. (A) ChR2 expression in ARC AgRP axons and photostimulation of their terminals in PVN-containing brain slices from AgRP-Cre mice. Inset: representative image showing whole-cell recording from a PVN neuron with the recording pipette indicated. (B) ChR2 expression in ARC AgRP neurons of AgRP-Cre mice (scale bar: 100 μm). (C) Synaptic projections of arcuate AgRP neurons to the PVN. (D--G) Representative electrophysiological recording traces obtained under baseline conditions and after application of pharmacological agents: dopamine, leptin, the kappa opioid receptor agonist U50,488, and the MC4R agonist MTII (H--K). Effects of pharmacological agents on ARC AgRP→PVN synaptic responses: (H) dopamine, (I) leptin, (J) U50,488, and (K) MTII. Each line represents individual neurons (Dopamine n=8; Leptin n=7; U50,488 n= 8; MTII n=8 neurons; 5 mice were used in each groups. (Data are mean ± standard deviation. Statistical analysis: Student's paired t-test; *p<0.05, **p<0.01)

(pH 7.35) and subsequently decapitated. Brains were extracted, post-fixed in the same solution for 4 h, and then cryoprotected overnight in 30% sucrose. Coronal sections (60 μm) were prepared using a vibratome and permeabilized in 0.1% Triton-X in PBS for 1 h at 4 °C. After rinsing, sections were mounted onto microscope slides and coverslipped with Fluoromount (Sigma, F4680, MO, USA). Confocal images were acquired using a Carl Zeiss microscope (Thornwood, NY, USA) [19].

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, USA). The normality of paired differences was assessed using the Shapiro–Wilk test before applying parametric tests. Since the assumption of normality was satisfied, comparisons between baseline and pharmacological conditions were performed using Student's paired t-test. Data are presented as mean ± standard deviation (SD). Exact p-values are reported throughout the manuscript, and $p<0.05$ is considered statistically significant. Post hoc power analyses were conducted using G*Power based on the observed effect sizes (Cohen's dz) for paired comparisons (two-tailed, $\alpha = 0.05$). Power analysis, effect size calculations, and normality test results are provided in the Supplementary Materials.

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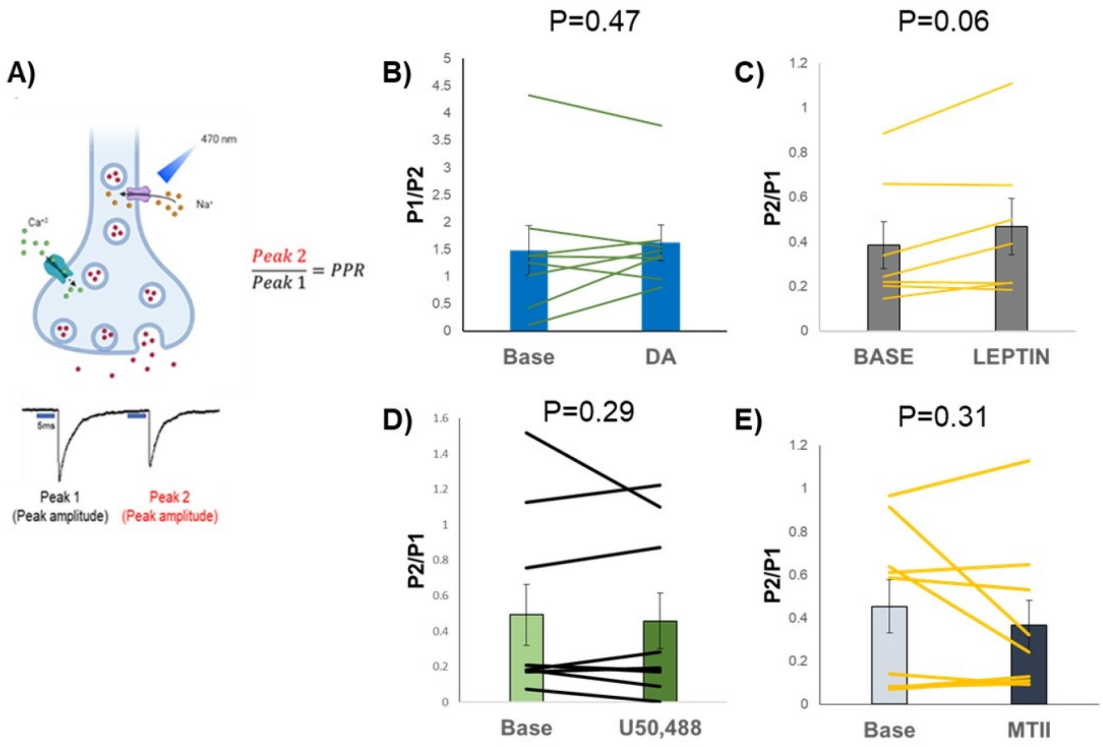

Figure 2. Effects of pharmacological agents on presynaptic release probability in the ARC AgRP→PVN pathway. (A) Schematic illustration of paired-pulse ratio (PPR; P2/P1) used to estimate neurotransmitter release probability. (B–E) Effects of pharmacological agents on PPR: (B) dopamine, (C) leptin, (D) the kappa opioid receptor agonist U50,488, and (E) the MC4R agonist MTII. Each line represents individual neurons (Dopamine n=8; Leptin n=7; U50,488 n= 8; MTII n=8 neurons; 5 mice were used in each groups. (Data are mean ± standard deviation).

RESULTS

Effects of pharmacological agents on peak amplitude in ARC$^{AgRP\rightarrow PVN}$ synaptic connectivity

To examine the pharmacological modulation of the ARC AgRP→PVN pathway, we employed channelrhodopsin-assisted circuit mapping (CRACM) to selectively isolate AgRP axon–mediated synaptic responses in PVN neurons. An AAV-FLEX-ChR2 vector was stereotaxically delivered into the arcuate nucleus of AgRP-Cre mice, and whole-cell patch-clamp recordings were subsequently performed on PVN neurons in acute hypothalamic slices. Laser stimulation (10 Hz, 2 pulses) targeting AgRP terminals evoked postsynaptic currents (Figure 1A–C). After establishing a 5-min baseline recording, pharmacological agents were bath-applied and responses were monitored for an additional 15 min (Figure 1D–G). Application of dopamine (50 μM) did not significantly modify the peak amplitude of light-evoked responses in the ARC AgRP→PVN pathway (Figure 1H). In contrast, leptin (100 nM) produced a significant reduction in response amplitude relative to baseline recordings (Figure 1I). To evaluate the potential contribution of opioid signaling, the kappa opioid receptor agonist U50,488 (2 μM) was applied to the bath solution. Activation of kappa opioid receptors significantly reduced the amplitude of optogenetically evoked currents (Figure 1J), consistent with a weakening of synaptic transmission in the ARC AgRP→PVN circuit. By comparison, application of the MC4R agonist MTII (100 nM) did not produce a detectable change in evoked responses relative to baseline conditions (Figure 1K). Post hoc power analyses (two-tailed, $\alpha = 0.05$) revealed low power for dopamine (dz = 0.19, power = 0.075) and MTII (dz = 0.08, power = 0.055), intermediate power for leptin (dz = 0.96, power = 0.57), and high power for U50,488 (dz = 1.8, power = 0.99).

Effects of pharmacological agents on the probability of GABA release

To determine whether the observed pharmacological effects on ARC AgRP→PVN synaptic transmission involve changes in presynaptic neurotransmitter release, we analyzed the paired-pulse ratio (PPR) as an indicator of release probability. Whole-cell recordings were performed in the presence of glutamate receptor antagonists (AP5 and CNQX) to isolate inhibitory postsynaptic currents (IPSCs) (Figure 2A). Paired-pulse photostimulation (470 nm; 2 × 5 ms pulses at 10 Hz) was applied to ChR2-expressing AgRP axon terminals in the PVN. Under these conditions, the P2/P1 ratio was used to assess potential changes in presynaptic release probability. Application of dopamine, leptin, the kappa opioid receptor agonist U50,488, and the MC4R agonist MTII did not significantly alter the paired-pulse ratio compared with baseline recordings (Figure 2B–E), indicating that these pharmacological manipulations do not significantly affect the probability of GABA release from AgRP presynaptic terminals in the ARC AgRP→PVN pathway.

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DISCUSSION

In this study, we investigated the effects of several neuromodulatory signals, including dopamine, leptin, the kappa opioid receptor agonist U50,488, and the melanocortin receptor agonist MTII, on synaptic transmission in the ARC AgRP→PVN pathway. This circuit represents a critical component of hypothalamic networks regulating appetite, body weight, and energy homeostasis [20-22].

Our results demonstrate that leptin and the activation of kappa-opioid receptors significantly suppress the peak amplitude of ARC AgRP→PVN synaptic transmission. In contrast, neither dopamine nor the melanocortin receptor agonist MTII significantly altered synaptic peak amplitude. These findings indicate that specific neuromodulatory systems can differentially regulate synaptic strength within this key hypothalamic feeding circuit.

Leptin is a well-established anorexigenic hormone that engages multiple hypothalamic nuclei to reduce food intake and enhance energy expenditure [11]. Previous studies have shown that leptin can directly inhibit AgRP neuron activity and reduce their orexigenic output [23]. Our data extend these findings by demonstrating that leptin also suppresses the synaptic efficacy of AgRP neuron projections to the PVN, suggesting a dual mechanism by which leptin can inhibit feeding: both by reducing AgRP neuron firing and by weakening their downstream synaptic influence on PVN neurons. This is consistent with reports that leptin signaling in the ARC is essential for the long-term regulation of energy balance and that leptin resistance in this region contributes to obesity [19,23]. Importantly, these findings provide direct electrophysiological evidence that leptin can weaken synaptic transmission from AgRP neurons to PVN neurons, revealing a circuit-level mechanism through which leptin may regulate feeding behavior.

Activation of the kappa opioid receptor (KOR) significantly reduced the peak amplitude of optogenetically evoked synaptic responses in the ARC AgRP→PVN pathway. This finding indicates that KOR activation suppresses synaptic transmission between AgRP and PVN neurons. Opioid signaling has been implicated in the regulation of feeding behavior, reward processing, and stress-related responses, and KOR activation has been shown to influence neuronal activity in brain regions involved in energy balance and motivational states [24-26]. Our results extend these observations by demonstrating that activation of KOR signaling can directly modulate synaptic strength within the ARC AgRP→PVN circuit, suggesting that kappa opioid pathways may participate in the regulation of hypothalamic feeding networks.

In contrast, activation of melanocortin receptors with the agonist MTII did not significantly affect synaptic transmission in the ARC AgRP→PVN pathway. Melanocortin signaling, particularly through MC4R-expressing PVN neurons, is widely recognized as a major regulator of appetite and energy expenditure [27]. The lack of acute synaptic modulation observed in our recordings suggests that MTII may influence feeding behavior primarily through mechanisms other than direct modulation of AgRP→PVN synaptic strength. For example, melanocortin signaling may act by altering the intrinsic excitability of PVN neurons or through network-level modulation involving additional hypothalamic circuits [28].

Interestingly, dopamine did not significantly affect ARC AgRP→PVN synaptic transmission in our experiments. Dopamine is a key neuromodulator of reward and motivation, and its role in feeding behavior is well established [29,30]. However, its direct effects on AgRP neuron synaptic output have not been clearly defined. Our results suggest that, at least acutely and in the context of the ARC AgRP→PVN pathway, dopamine does not modulate synaptic strength, although it may influence feeding behavior through other circuits or via longer-term mechanisms.

Furthermore, analysis of paired-pulse ratio (PPR) revealed that none of the tested agents significantly altered the probability of GABA release from AgRP presynaptic terminals onto PVN neurons [31]. This finding indicates that the observed changes in synaptic peak amplitude are unlikely to arise from alterations in presynaptic release probability. Instead, these effects may reflect postsynaptic mechanisms or changes in synaptic efficacy within the ARC AgRP→PVN circuit. Previous studies have shown that AgRP neurons release both GABA and NPY to inhibit PVN neurons and promote feeding behavior [1], suggesting that multiple signaling mechanisms contribute to the regulation of this pathway.

Limitations

The experiments were performed in acute brain slices, which may not fully reflect in vivo circuit dynamics. In addition, the pharmacological manipulations represent acute effects and may not capture long-term regulatory mechanisms. Further studies are required to clarify the precise cellular mechanisms underlying the observed synaptic modulation.

CONCLUSION

Overall, our findings highlight the complex neuromodulatory regulation of the ARC AgRP→PVN circuit and identify leptin and kappa opioid receptor signaling as important modulators of synaptic transmission within this pathway. These results provide new insights into the synaptic mechanisms underlying the hypothalamic control of feeding behavior and may inform the development of therapeutic strategies targeting hypothalamic circuits implicated in obesity and metabolic disorders.

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Ethics Committee Approval: All experimental protocols were reviewed and approved by the Yeditepe University Experi-

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mental Animal Research Ethics Committee (Decision No: 2023/11-06, Date: 09.11.2023).

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Conflict of Interest: The authors declare no conflicts of interest.

Author Contributions: YY: Performed electrophysiological recordings, imaging, and surgeries; BY and YY: Conceived experiments, analyzed data, and wrote the manuscript.

Financial Disclosure: No financial support was obtained for this study.

Data availability: Data will be made available on request.

Artificial Intelligence Disclosure: ChatGPT (OpenAI, GPT-5.5) was used solely for language editing and to improve readability in the Abstract and Discussion sections during manuscript preparation. The AI tool was not involved in the study design, data analysis, interpretation of results, or the generation of scientific conclusions. All content was carefully reviewed, validated, and approved by the authors, who retain full responsibility for the manuscript.

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