Adiponectin Depolarizes Parvocellular Paraventricular Nucleus Neurons Controlling Neuroendocrine and Autonomic Function

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Adiponectin plays important roles in the control of energy homeostasis and autonomic function through peripheral and central nervous system actions. The paraventricular nucleus (PVN) of the hypothalamus is a primary site of neuroendocrine (NE) and autonomic integration, and, thus, a potential target for adiponectin actions. Here, we investigate actions of adiponectin on parvocellular PVN neurons. Adiponectin influenced the majority (65%) of parvocellular PVN neurons, depolarizing 47%, whereas hyperpolarizing 18% of neurons tested. Post hoc identification (single-cell RT-PCR) after recordings revealed that adiponectin depolarizes NE-CRH neurons, whereas intracerebroventricular injections of adiponectin in vivo caused increased plasma ACTH concentrations. Adiponectin also depolarized the majority of TRH neurons, however, NE-TRH neurons were unaffected, in accordance with in vivo experiments showing that intracerebroventricular adiponectin was without effect on plasma TSH. In addition, bath administration of adiponectin also depolarized both preautonomic TRH and oxytocin neurons. These results show that adiponectin acts in the central nervous system to coordinate NE and autonomic function through actions on specific functional groups of PVN neurons. (Endocrinology 150: 832–840, 2009)

Energy homeostasis is coordinated in large part through peripherally produced hormones that interact with the central nervous system (CNS) (1). Adipose tissues produce a number of these signaling molecules that function in the CNS to dictate feeding patterns and responses to stress, and maintain dynamic equilibrium. Adiponectin is one such protein that, like leptin and resistin, is produced by adipocytes, circulates in the plasma, and controls network excitability in important autonomic nuclei (2–6). However, unlike leptin and resistin, adiponectin circulates at extremely high concentrations that vary inversely with adiposity (7, 8). Adiponectin knockout mice show impaired responses to glucose challenges, and have compromised insulin and metabolic function among other pathologies (9). When injected into the brain, adiponectin has a marked effect on autonomic function. Mice show a substantial decrease in body weight, increased thermogenesis, increased oxygen consumption, and increased CRH mRNA production in the paraventricular nucleus (PVN) (10).

This evidence suggests that adiponectin plays a critical role in controlling energy homeostasis.

Adiponectin signals through two known receptors: adiponectin receptors (AdipoRs) 1 and 2 (11). AdipoRs are located throughout the CNS, notably in regions of the hypothalamus and brainstem, important in controlling autonomic function and feeding behavior, including the area postrema (12), arcuate nucleus (13), and the PVN (3).

The PVN contains neurons that play important roles in controlling autonomic state (14, 15). Electrophysiologically, the PVN can be divided into three populations of neurons (16, 17): magnocellular (MNC), preautonomic (PA) parvocellular, and neuroendocrine (NE) parvocellular. Distinct groups of PA and NE neurons contain CRH, TRH, and oxytocin (OT) that participate as neuromodulators (PA) or hormones (NE) translating output information from the PVN to its targets (15).

We recently reported that adiponectin controls the excitability of PVN MNC neurons; hyperpolarizing OT neurons, having...
varying effects on vasopressin neurons and having no effect on neurons that expressed both peptides (3). Here, we examine the effects of adiponectin on the parvocellular neurons in the PVN (PA and NE), specifically investigating three chemically distinct types of neurons within this group: CRH-, TRH- and OT-expressing cells, while also correlating electrophysiological effects with integrated NE function in conscious freely moving animals.

Materials and Methods

All procedures involving the use of animals conformed to the standards of the Canadian Counsel on Animal Care and were approved by the Queen’s University Animal Care Committee. All chemicals used in making solutions were obtained from Sigma Pharmaceuticals (Oakville, Ontario, Canada). Tetrodotoxin (TTX) citrate was obtained from Alomone Laboratories (Jerusalem, Israel), made into working aliquots, and stored at −80°C. Globular adiponectin was obtained from Phoenix Pharmaceuticals (Belmont, CA), made into working aliquots, and stored at −20°C until experimentation.

Electrophysiology

Coronal hypothalamic slices (300 μm) containing the PVN were taken daily from male Sprague Dawley rats (Charles River, Quebec, Canada) between postnatal day 19 and 26 that were maintained on a 12-h light, 12-h dark cycle, and provided with food and water ad libitum. Rats were decapitated, and brains were removed and placed in ice-cold slicing solution consisting of (in mM) 87 NaCl, 2.5 KCl, 25 NaHCO3, 0.5 CaCl2, 7 MgCl2, 1.25 NaH2PO4, 25 glucose, and 75 sucrose bubbled with 95% O2/5% CO2 for 3–5 min. Brains were then trimmed to size, mounted, immersed with slicing solutions, and 300 μm hypothalamic slices containing PVN (typically three) were cut using a vibratome (Leica, Nussloch, Germany). Slices were then bisected and incubated at 32.5°C until experimentation. Endocrinology, February 2009, 150(2):832–840 endo.endojournals.org

Current clamp recordings from parvocellular PVN neurons were obtained following the formation of a GΩ seal by applying negative pressure to the pipette tip. Cells that failed to form outside-out patches were eliminated from the data set if they did not show at least partial recovery to baseline.

Single-cell RT-PCR

After experimentation a post hoc single-cell RT-PCR was performed to detect mRNA for prominent neuropeptides expressed in parvocellular neurons (Table 1). Gentle suction was applied to the recording pipette to aspirate cytoplasm. Membrane resistance was continuously monitored as an outside-out patch was pulled, sealing the cytoplasmic contents within the pipette. Cells that failed to form outside-out patches were eliminated from sense-specific RT-PCR analysis but were included in the analysis of changes in membrane potential. After pipette withdrawal from the bath, the electrode tip was broken, and its contents were expelled into a 0.5-ml PCR tube. The following were added to the tube to set up the deoxyribonucleic acid (DNA)ase reaction: (approximate concentrations) 10 U DNase, 10 μM 100X reaction buffer with MgCl2 (Fermentas Life Sciences, Burlington, Ontario, Canada) and incubated at 37°C for 30 min. After incubation, 2.5 μM EDTA was added and incubated at 65°C for 10 min to stop the DNase reaction. Reverse transcriptase reaction proceeded immediately after by adding dithiothreitol (26 mM), deoxyribonucleotide triphosphates (3 mM), random hexamers (3 μM), MgCl2 (4 mM), ribonuclease inhibitor (20 U), and SuperScript II (100 U) (Invitrogen Canada, Burlington, Ontario, Canada), and allowed to incubate overnight at 37°C to allow the reaction to proceed. A negative control reaction in which SuperScript II was omitted from the reaction mixture was also performed. Samples were stored at −80°C until the multiplex reaction.

A multiplex PCR strategy was used to amplify the cDNA produced in the reverse transcriptase reaction. This protocol consisted of two different amplification steps: outside and nested. First, primer sets (0.2 μM) specific for all genes of interest (outside) were added to the cDNA from the single cell, which then underwent an amplification protocol. Reactions were performed in 100-μl volumes with reagents provided in the Qiagen Multiplex kit (Qiagen, Mississauga, Ontario, Canada). The reaction mixture was denatured at 95°C for 15 min, then cycled 20 times through a temperature protocol of 94°C for 30 sec, 60°C for 90 sec, and 72°C for 90 sec. The second step consisted of individual reactions for each gene of interest using “nested” primer sets. Reactions were performed in 50-μl volumes consisting of Qiagen Multiplex reaction reagents, 0.2 μM primers and 2 μl solution from the multiplex reaction to act as template. The reaction mixture was subject to 35 cycles of the same amplification protocol. Two control reactions were performed during the multiplex protocol: 1) 1 reaction was run with PCR H2O instead of cDNA to detect for genomic contamination, and 2) a second reaction was run with cDNA from whole PVN to assess primer integrity and eliminate false negatives. PCR products from the nested reaction were run on a 2% (wt/vol) agarose gel containing ethidium bromide and sequenced to confirm their identity (Robarts Research Institute, London, Ontario, Canada). PCRs that failed to pass any of the control tests were eliminated from the study.
**In vivo experiments**

Under ketamine (Ketaset; Fort Dodge Animal Health, Fort Dodge, IA)/xylazine (TranquiVed; Vedco Inc., St. Joseph, MO) anesthesia (60 mg/8 mg mixture/ml, 0.1 ml/100 g body weight, ip injection), rats were placed in a stereotaxic device, and a 23-gauge, stainless steel cannula (17 mm) was implanted into the right lateral cerebroventricle as previously described (19). Minimally, 5 d later, after the animals had returned to preimplantation body weights, an indwelling jugular vein cannula was implanted as previously described (20) under isoflurane-induced anesthesia (3% in O2 for induction, 2% in O2 for maintenance of anesthesia; IsoSol; Vedco). The jugular cannula was exteriorized at the back of the neck and sealed with heparinized saline (200 U/ml 0.9% NaCl). On the following day, an extension tubing (PE-50) was attached to the jugular cannula to facilitate blood sampling, and rats were left undisturbed for minimally 120 min. An initial blood sample was then withdrawn from the jugular vein without disturbing the animal. All blood samples (0.3 ml) were removed from conscious, unrestrained rats into heparinized syringes and replaced with an equal volume of 0.9% NaCl (37 C). Sampling was conducted between 0900 and 1100 h (lights on 0600 h). Blood samples were stored on ice before plasma was separated (10,000 \( \times \) g, 5 min) and stored at -20 C until hormone assays were conducted. Immediately after the removal of the initial (zero time) blood sample, a 2-\( \mu \)l injection of isotonic saline vehicle alone or vehicle containing 0.1, 0.3, or 1.0 nmol adiponectin was conducted via the indwelling cerebroventricular cannula. Subsequent blood samples were removed 5, 15, 30, and 60 min after intracerebroventricular (icv) injections.

Plasma TSH levels were measured (20 \( \mu \)l aliquots) using the materials obtained from the National Peptide and Pituitary Program (National Institutes of Health (rTSH-RP-2 standard, minimum detectable level: 0.5 ng/ml; interassay and intraassay coefficients of variability were less than 8%). ACTH concentrations in plasma (33 \( \mu \)l aliquots) were determined by RIA using the unextracted plasma protocol described by the supplier (Peninsula Laboratories, Inc., San Carlos, CA).

### TABLE 1. Primer sets used in the detection of mRNA from single cells

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer</th>
<th>Position</th>
<th>Sequence</th>
<th>Product size (bp)</th>
<th>Accession no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceraldehyde-3-phosphate dehydrogenase</td>
<td>GAPDH</td>
<td>F (outside) R</td>
<td>gatggtaaggtgtgccgttctg cccagtctgccttcctctt</td>
<td>469</td>
<td>NM_017008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R (nested)</td>
<td>ggcattaagctcggtttgctg</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>γ-Amino butyric acid</td>
<td>GAD67</td>
<td>F (outside) R</td>
<td>ctctgtgctctcacccttcatc caaacaactgagccgctagaa</td>
<td>550</td>
<td>NM_017007</td>
</tr>
<tr>
<td>Tyrosine hydroxylase</td>
<td>TH</td>
<td>F (outside) R</td>
<td>ccacctgtagatatttttgtgcg cccagtgtgctctcactctg</td>
<td>1138</td>
<td>NM_012740</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>VP</td>
<td>F (outside) R</td>
<td>acctctacctctctgctctactctc taagccgctgacgctgctt</td>
<td>237</td>
<td>NM_016992</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>OT</td>
<td>F (outside) R</td>
<td>acctctacctctctgctctactctc taagccgctgacgctgctt</td>
<td>237</td>
<td>NM_016992</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone</td>
<td>CRH</td>
<td>F (outside) R</td>
<td>acctctacctctctgctctactctc taagccgctgacgctgctt</td>
<td>237</td>
<td>NM_016992</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone</td>
<td>TRH</td>
<td>F (outside) R</td>
<td>acctctacctctctgctctactctc taagccgctgacgctgctt</td>
<td>237</td>
<td>NM_016992</td>
</tr>
<tr>
<td>Vesicular glutamate transporter-2</td>
<td>VGLUT2</td>
<td>F (outside) R</td>
<td>acctctacctctctgctctactctc taagccgctgacgctgctt</td>
<td>237</td>
<td>NM_016992</td>
</tr>
<tr>
<td>Adiponectin receptor 1</td>
<td>AdipoR1</td>
<td>F (outside) R</td>
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<td>583</td>
<td>AF271235</td>
</tr>
<tr>
<td>Adiponectin receptor 2</td>
<td>AdipoR2</td>
<td>F (outside) R</td>
<td>ggctcctctacgacgtaacttggagaa</td>
<td>583</td>
<td>AF271235</td>
</tr>
</tbody>
</table>

F, Forward; R, reverse.
CA). Minimum detectable ACTH levels were 1 pg/ml, and interassay and intraassay coefficients of variability were less than 8%.

Data from the RIAs were analyzed by one-way ANOVA both within treatment groups across time and between treatment groups at any sampling time point, followed by Scheffe’s multiple comparison testing. Homogeneity of variance was established using the S test. Significance was assigned to results that occurred with less than 5% probability.

Results

Adiponectin influences the excitability of parvocellular neurons in the PVN

Current clamp recordings were obtained from 122 identified (58 PA and 64 NE) parvocellular PVN neurons, and the effects

FIG. 1. Adiponectin effects on the membrane potential of NE and PA neurons in the PVN. A, Bath administration of 10 nM adiponectin (black bar) induces both depolarizing (i) and hyperpolarizing (ii) effects on membrane potential in different populations of type 3 NE neurons. Membrane potential routinely recovered to near control membrane potential (red line) after removal of adiponectin from the bath. B, Similar effects of adiponectin on membrane potential were seen in type 2 PA neurons, depolarizing (i) a population of cells while hyperpolarizing (ii) a separate group of neurons.
Adiponectin depolarizes PA TRH neurons

We also obtained current clamp recordings from a total of 10 neurons that were identified post hoc as TRH mRNA expressing neurons in which we were able to assess the effects of bath administration of 10 nM adiponectin. The majority of TRH neurons (six of 10) depolarized in response to 10 nM adiponectin (7.6 ± 1.9 mV) (Fig. 4A). More interestingly, classification of TRH neurons as NE or PA revealed that a majority of the TRH neurons depolarized by adiponectin were PA cells (six of seven), whereas zero of three NE TRH neurons were affected by adiponectin (Fig. 4B). Analysis of the expression patterns of AdipoRs in TRH neurons showed that one of six responsive PA TRH neurons expressed receptors (R1, n = 3; R2, n = 1; and R1/R2, n = 3). We hypothesized that this may be due to the effect of adiponectin on a presynaptic interneuron and, therefore, performed additional current clamp recordings from a total of four identified PA TRH neurons that did not express either AdipoR (4.0 ± 2.9 mV, n = 5) did not. We hypothesized that adiponectin acts on CRH neurons in the PVN to control CRH release from the median eminence, and subsequent ACTH release from the anterior pituitary gland.

Adiponectin depolarizes NE CRH neurons

To assess adiponectin’s effects on specific groups of neurons in the PVN after membrane potential recordings, we performed post hoc single-cell RT-PCR analysis for markers of interest (Table 1). Of the 122 neurons recorded from, 13 were positively identified as CRH mRNA expressing neurons. Of 13 CRH neurons, 10 were NE neurons, and 70% of those neurons showed a depolarizing shift in membrane potential in response to 10 nM adiponectin (5.2 ± 1.1 mV) (Fig. 3, A and B). In addition, three PA CRH neurons responded to 10 nM adiponectin (two depolarized, one hyperpolarized).

AdipoR profile in CRH NE neurons was also assessed by single-cell RT-PCR, and all seven of the responding CRH neurons expressed mRNA for at least one AdipoR (R1, n = 3; R2, n = 1; and R1/R2, n = 3). NE CRH neurons that did not express either receptor did not respond to adiponectin (0.7 ± 0.9 mV, n = 3).

We next examined the effect of adiponectin on the hypothalamic-pituitary-adrenal axis by measuring the effects of adiponectin injected into the lateral cerebroventricle (icv) on plasma ACTH concentrations. Injections (icv) of adiponectin caused a dose-related increase in plasma ACTH concentrations 1.5 and 30 min after injections when compared with saline-injected controls (Fig. 3C). The injection of 1.0 nmole adiponectin showed the largest increase in plasma ACTH concentration compared with vehicle at 15 min [22.3 ± 3.7 pg/ml (1.0 nmole adiponectin) vs. 8.6 ± 1.0 pg/ml (vehicle); P = 0.014], (ANOVA, Scheffe multiple comparisons)]. Plasma ACTH concentrations had returned to baseline at the 60-min time point, suggesting that the actions of adiponectin are transient and reversible. These results indicate that adiponectin acts on CRH neurons in the PVN to control CRH release from the median eminence, and subsequent ACTH release from the anterior pituitary gland.

FIG. 2. The effects of adiponectin are direct and proportionally similar across parvocellular PVN neurons. A, Histogram showing percentage of each cell type; NE, PA, total combined and when action potential induced neurotransmitter release was inhibited through the application of 1 μM TTX of neurons depolarizing (blue) or hyperpolarizing (red) in the presence of 10 nM adiponectin. B, Summary box and whisker plot indicating for both depolarization and hyperpolarization the smallest observation, the lowest quartile, median, upper quartile, and the largest observation in each data set. The median depolarization was 5.5 mV, whereas the median hyperpolarization was −5.7 mV.
Adiponectin or time point (15 min, vehicle: 8.8 ng/ml vs. 1.0 nmole: 7.8 ng/ml, ANOVA, Scheffe’ multiple comparisons) after adiponectin administration. These data suggest that adiponectin selectively regulates ACTH secretion in the hypothalamic-pituitary axis but has no effect on TRH/TSH secretion.

Adiponectin depolarizes PA OT neurons
A significant proportion of PA neurons that express OT send axonal projections to the nucleus of the solitary tract (NTS), and have been suggested to modify feeding by sensitizing NTS neurons to satiety signals such as cholecystokinin (21). We recorded from 15 PA neurons that were positively identified as OT expressing neurons. The majority of these PA OT neurons (11/15) depolarized in response to 10 nM adiponectin (4.1 ± 0.4 mV) (Fig. 5), whereas one of the remaining four cells tested was hyperpolarized by peptide administration. These data suggest that adiponectin selectively regulates ACTH secretion in the hypothalamic-pituitary axis but has no effect on TRH/TSH secretion.

Discussion
These data show both endocrine and autonomic effects of adiponectin acting upon specific groups of neurons in the PVN, confirming and identifying new and potentially critical roles played by this peptide in regulating energy and autonomic homeostasis. We have shown that adiponectin is primarily an excitatory peptide in the parvocellular regions of the PVN, depolarizing a majority of identified parvocellular neurons, while hyperpolarizing only a minority of neurons in the same groups. We have also shown that adiponectin directly excites NE CRH neurons that express AdipoRs, leading potentially to an increase in CRH release into pituitary portal circulation. Indeed, we have measured an increase in plasma ACTH concentrations after lateral cerebroventricular injections of adiponectin.

In addition, we have identified two chemically distinct groups of PA neurons: TRH expressing and OT expressing cells whose electrical excitability is controlled by adiponectin, suggesting that the peptide may play alternate regulatory roles in addition to hypothalamic-pituitary axis induction through modulation of caudally projecting, PA cells.

CRH is a potent anorexigenic peptide that when released from parvocellular neurons into the median eminence, regulates the secretion of ACTH from anterior pituitary cells, ultimately
controlling plasma glucocorticoid levels (22). Our observations that adiponectin depolarizes the majority of NE CRH neurons while also increasing plasma concentrations of ACTH suggests mechanisms through which this peptide may control activation of the stress axis. Previous reports indicate that when injected intracerebroventricularly, adiponectin increases respiration, energy metabolism, and body temperature in mice (10), all indicators of elevated sympathetic tone. Intriguingly, iv injections of adiponectin increase feeding through actions at the arcuate nucleus (13), which has recently been shown to express AdipoR1 and AdipoR2 (23), suggesting a site specificity for autonomic function. Our results clarify the mechanism responsible for this, and suggest that adiponectin’s actions at CRH neurons involved in the hypothalamic-pituitary axis partially dictate the metabolic and autonomic state of the animal.

PVN TRH neurons also control feeding behavior, participate in the stress response, and control metabolic function (24). Increases in TRH secretion at the median eminence are associated with elevated thyroid function ultimately increasing the drive to promote negative energy expenditure. Given that iv injections of adiponectin increase energy expenditure (10), we were surprised to find that plasma concentrations of TSH after central adiponectin injections were unchanged, an observation that ultimately correlates well with our electrophysiological data showing that the TRH NE cells tested were also unaffected by adiponectin.

In contrast to neurosecretory TRH neurons, PA TRH neurons were selectively depolarized by adiponectin. These neurons have been suggested to project to autonomic preganglionic neurons in the dorsal vagal complex (18) and spinal cord, and send information about core body temperature to peripheral targets (25). Thus, adipocyte derived adiponectin acting through PA TRH neurons may represent a vital connection coupling adiposity stores to central thermoregulation. Although an attractive hypothesis, further experiments will be needed to investigate this possibility.

Activation of PA OT neurons that project to the NTS has exerted profound effects on feeding patterns (21). The excitation of these PVN neurons leading to the release of OT into the hind-brain promotes the sensitization of NTS neurons to satiety cues such as cholecystokinin, advancing meal termination (26). The depolarizing effect of adiponectin on PA OT neurons would suggest that adiponectin may act centrally to control meal size. These effects would have profound consequences on feeding behavior and may contribute to the effects seen on weight loss when adiponectin is injected intracerebroventricularly (10). The effect of adiponectin on PA OT neurons may not be limited to alterations in feeding behavior but may be heterogeneous in nature. Caudally projecting PA neurons have functionally diverse roles in the autonomic nervous system (27, 28), and further experiments will be needed to examine other systems.

Intriguingly, the depolarizing effects of adiponectin on type 2 PA OT neurons are in contrast to adiponectin’s hyperpolarizing effects on PVN OT MNC neurons (3). Although these are two functionally and anatomically independent systems, they share the same signaling molecule OT and apparently are differentially modulated by adiponectin. Together, these data would indicate that the function of adiponectin in the PVN may not be to control the release of a specific peptide but to coordinate diverse networks of neurons that may use the same signaling molecule but have unique targets and, thus, different effects in vivo. The effective ivc dose of adiponectin was 1 nmole, a gram per body weight value similar to that used in previous in vivo studies (10). Assuming a 1-ml volume of cerebral spinal fluid (CSF), the calculated CSF concentration of adiponectin is 1 μM. Although this concentration is larger than the 10 nm used in the in vitro current clamp studies, enzymatic degradation and diffusion to the presumed active site in PVN will both result in further reductions in the active concentration reaching the PVN. These considerations suggest that our ivc injections likely achieve concentrations in PVN that are closer to the 10-nm concentration used in vitro.

Adiponectin is unlikely to cross the blood-brain barrier (29, 30), however, concentrations of the peptide have been detected in the CSF of humans and rats (31, 32), and CSF levels have increased upon iv injections of the peptide (10, 23). These data prompt speculation as to the source of the adiponectin for actions in the CNS. Recent evidence suggests that adiponectin mRNA is
readily expressed in chicken and mouse brain (33, 34). Although we cannot exclude that peripherally derived adiponectin controls the excitability of CNS structures, the case for brain-derived adiponectin as a modulator of these systems is an attractive alternative hypothesis and may play an important role in vivo.

Our data correlating AdipoR expression with cell responsiveness confirm previous reports from our laboratory (3, 12) showing that neurons expressing AdipoR1/R2, AdipoR1 alone, or AdipoR2 alone all respond to adiponectin. Similarly, all responding CRH neurons expressed at least one AdipoR. These observations suggest that the response of the neuron to adiponectin may not be dictated by receptor expression but, rather, by the ion channel(s) targets expressed by the neuron and modulated by activation of receptor(s). Elucidation of these target ion channels will provide more information on the intracellular signaling mechanisms responsible for adiponectin induced neuronal excitability.

Several PA neurons that expressed TRH or OT and responded to adiponectin did not express mRNA for either AdipoR. However, the response to adiponectin in these neurons was maintained in TTX, suggesting an effect, independent of AdipoR activation at the cell surface of these recorded neurons. Several possibilities could explain these observations. Leptin and ghrelin have been shown to confer their central effects on feeding through activation of the PVN endocannabinoid system, leptin specifically reducing excitatory synaptic drive to PVN neurons through an endocannabinoid-dependent fast inhibitory feedback mechanism (35, 36). Whether adiponectin also signals through the endocannabinoid system is unknown at the current time but could represent a receptor-independent mechanism of signaling in these neurons. A second possibility of how adiponectin could influence specific groups of neurons in the parvocellular regions of the PVN, depolarizing NE CRH, PA TRH, and PA OT neurons. Furthermore, through in vivo studies, we have shown that when injected centrally, adiponectin selectively controls the release of ACTH into the plasma while having no effect on TSH release.

This study highlights the diverse central roles played by adiponectin in controlling energy homeostasis and autonomic function, and may provide insight into the pathophysiology of disrupted adiponectin signaling in diabetes and obesity.

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