Research

Inhibiting ventral hippocampal NMDA receptors and *Arc* increases energy intake in male rats

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Research into the neural mechanisms that underlie higher-order cognitive control of eating behavior suggests that ventral hippocampal (vHC) neurons, which are critical for emotional memory, also inhibit energy intake. We showed previously that optogenetically inhibiting vHC glutamatergic neurons during the early postprandial period, when the memory of the meal would be undergoing consolidation, caused rats to eat their next meal sooner and to eat more during that next meal when the neurons were no longer inhibited. The present research determined whether manipulations known to interfere with synaptic plasticity and memory when given pretraining would increase energy intake when given prior to ingestion. Specifically, we tested the effects of blocking vHC glutamatergic N-methyl-D-aspartate receptors (NMDARs) and activity-regulated cytoskeleton-associated protein (*Arc*) on sucrose ingestion. The results showed that male rats consumed a larger sucrose meal on days when they were given vHC infusions of the NMDAR antagonist APV or *Arc* antisense oligodeoxynu-cleotides than on days when they were given control infusions. The rats did not accommodate for that increase by delaying the onset of their next sucrose meal (i.e., decreased satiety ratio) or by eating less during the next meal. These data suggest that vHC NMDARs and *Arc* limit meal size and inhibit meal initiation.

Research into the higher-order cognitive controls of eating behavior has demonstrated that hippocampal neurons, which are critical for learning and memory, also regulate energy intake (Benoit et al. 2010; Parent 2016; Kanoski and Grill 2017). The hippocampus is functionally divided along its longitudinal axis into dorsal (posterior in primates) and ventral (anterior in primates) poles (Moser and Moser 1998; Fanselow and Dong 2010; Strange et al. 2014). Generally, dorsal hippocampal (dHC) neurons are necessary for episodic and spatial memory, whereas ventral hippocampal (vHC) neurons are essential for affective and motivational processes and emotional memory (Fanselow and Dong 2010; Strange et al. 2014). dHC and vHC have different anatomical connections, cellular and circuit properties and patterns of gene expression that likely contribute to the different functions that they serve (Moser and Moser 1998; Thompson et al. 2008; Dong et al. 2009; Barkus et al. 2010; Fanselow and Dong 2010; Bienkowski et al. 2018).

vHC neurons, in particular, are poised to integrate energy-related signals with mnemonic processes because they contain receptors for numerous food-related signals (Kanoski and Grill 2017) and project to several brain regions critical for food intake (Namura et al. 1994; Cenquizca and Swanson 2006; Radley and Sawchenko 2011; Hsu et al. 2015b). vHC lesions increase food consumption and body mass (Davidson et al. 2009, 2012, 2013), and activation of vHC receptors for gut hormones affects food intake and food-related memory (Kanoski et al. 2011, 2013; Hsu et al. 2015a, 2017, 2018). Additionally, vHC glutamatergic projections to the bed nucleus of the stria terminalis, lateral septum, and prefrontal cortex inhibit energy intake (Sweeney and Yang 2015; Hsu et al. 2017).

It is possible that vHC neurons contribute to the representation of the memory of a meal and inhibit subsequent intake. In support, we have shown that vHC neurons inhibit energy intake during the postprandial period. Specifically, optogenetic inhibition of vHC principle glutamatergic neurons given after the end of a sucrose or chow meal, timed to occur when the memory of the meal would be undergoing consolidation, accelerates the onset of the next meal and increases the amount eaten during the next meal when the neurons are no longer inhibited (Hannapel et al. 2019). Inactivation of these neurons given after a saccharin meal also hastens the initiation of the next saccharin meal and increases the size of that next meal, suggesting that vHC inhibition does not increase intake by disrupting the processing of interoceptive visceral signals (Hannapel et al. 2019).

If vHC neurons inhibit intake through a process that involves memory, then well-defined molecular events necessary for vHC synaptic plasticity should play a role in controlling meal timing and meal size because synaptic plasticity at hippocampal excitatory synapses is a critical mechanism underlying memory formation (Bailey et al. 2015; Bartsch and Wulff 2015). Activation of glutamatergic N-methyl-D-aspartate receptors (NMDARs) is required for most forms of hippocampal synaptic plasticity (Malenka and Nicoll 1993; Volianskis et al. 2015). NMDAR-dependent increases in intracellular calcium activate proteins and stimulate mRNA synthesis and protein translation that collectively act to increase glutamate AMPA receptor function in the postsynaptic cell, thereby increasing glutamate signaling and synaptic strength (Shanley et al. 2001; Bevilaqua et al. 2005; Herring and Nicoll 2016). Synaptic plasticity in vHC is NMDAR-dependent and vHC NMDARs are often necessary for vHC-dependent memory (Zhang et al. 2001; Xu et al. 2005; Kent et al. 2007; Czerniawski et al. 2012; Portero-Tresserra et al. 2014; Zhu et al. 2014; Clark et al. 2015; Maggio et al. 2015). Of note, feeding-related hormones such as insulin and leptin enhance NMDAR functionality in hippocampal cultured neurons and slices (Liu et al. 1995; Shanley et al. 2001).

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Hippocampal synaptic plasticity is also dependent on the activation of the immediate early gene (IEG) activity-regulated cytoskeleton-associated protein (*Arc*). *Arc* is considered a master regulator of synaptic plasticity (Bramham et al. 2010; Korb and Finkbeiner 2011; Shepherd and Bear 2011). It is downstream from many molecular signaling pathways and is necessary for virtually every type of synaptic plasticity (Bramham et al. 2008; Korb and Finkbeiner 2011; Shepherd and Bear 2011). Learning experiences produce small but significant increases in *Arc* that are typically maximal within 15 min of the experience, and unlike other IEGs, *Arc* expression reflects synaptic plasticity rather than neuronal activity (Fletcher et al. 2006; Guzowski et al. 2006; Carpenter-Hyland et al. 2010). vHC *Arc* is necessary for memory consolidation because disrupting vHC *Arc* expression with *Arc* antisense (anti-*Arc*) oligodeoxynucleotides (ODN) disrupts vHC-dependent memory (Czerniawski et al. 2011, 2012; Chia and Otto 2013). We have shown that sucrose consumption increases vHC *Arc* expression during the early postprandial period (Hannapel et al. 2017), suggesting that ingestion activates molecular processes required for synaptic plasticity in vHC.

Although it is well established that vHC neurons influence energy regulation, it is unknown whether vHC neurons regulate energy intake through a process that requires NMDARs and *Arc*. In the present experiments, we tested the prediction that disrupting vHC NMDAR activation and *Arc* expression would increase meal size and decrease the interval between meals. Specifically, NMDAR antagonists or anti-*Arc* ODNs were infused into the vHC and subsequent intake of sucrose was assessed.

Results

Premeal inhibition of vHC NMDARs increases the amount of sucrose ingested during the first meal and disrupts the relationship between meal size and the timing and size of the next meal

Figure 1 depicts the placement of the cannulae in vHC (x represents the APV study). The results from the two sucrose exposure protocols were not significantly different (not shown) and were therefore combined. The data from two rats were excluded because the size of their first meal was more than two standard deviations from the mean, which resulted in a final sample size of 13 rats. The vHC infusions of the NMDAR antagonist APV given 15 min before access to sucrose (Fig. 2A) significantly increased the size

of the first postinfusion meal ($Z = 2.065$, $P = 0.039$) (Fig. 2B). The rats did not compensate for this increased intake by delaying the onset of their next meal because APV did not affect the postprandial intermeal interval (ppIMI; $Z = -1.098$, $P = 0.272$]) (Fig. 2C), but did significantly decrease the satiety ratio (i.e., ppIMI/size of first meal; $Z = -2.201$, $P = 0.028$) (Fig. 2D). The rats also failed to compensate by eating less during their next meal because the intra-vHC APV infusions did not significantly affect the size of the second meal ($Z = 0.489$, $P = 0.625$) (Fig. 2E). APV also did not affect the total number of meals consumed during the 4-h recording period ($Z = 1.395$, $P = 0.163$) (Fig. 2F), nor the total amount of sucrose ingested ($t_{(12)} = -1.389$, $P = 0.1.90$) (Fig. 2G).

Down-regulating *Arc* mRNA also increases the amount of sucrose consumed and disrupts the relationship between meal size and the timing and size of the next meal

Placement of the cannulae is depicted in Figure 1 (filled black circle represents the anti-*Arc* study). The data from seven rats were not included in the statistical analyses as a result of misplaced cannulae, resulting in a final sample size of nine rats. The results showed that down-regulating *Arc* in the vHC had a similar effect on sucrose intake as did blocking vHC NMDARs in experiment 1. Compared with vHC infusions of the scrambled control, the vHC infusions of the anti-*Arc* ODN (Fig. 3A) increased the size of the first postinfusion meal ($t_{(8)} = -2.304$, $P = 0.050$) (Fig. 3B) and the rats did not compensate for this larger meal by increasing the ppIMI ($Z = -0.1400$, $P = 0.9453$) (Fig. 3C), which resulted in a significant decrease in the satiety ratio ($Z = -2.1917$ $P = 0.0273$) (Fig. 3D). As in experiment 1, the rats also did not compensate for this increased intake during the first meal by eating less during the second one because the anti-*Arc* ODN did not affect the size of the second meal ($t_{(8)} = -0.129$, $P = 0.900$) (Fig. 3E). vHC infusions of the anti-*Arc* ODN also did not affect the number of meals consumed during the recording period ($Z = 1.101$, $P = 0.271$) (Fig. 3F), nor the total amount of sucrose consumed ($Z = -1.4809$, $P = 0.1641$) (Fig. 3G).

The quantitative real-time PCR (qRT-PCR) data showed that sucrose consumption increased vHC *Arc* expression (Fig. 4). More importantly, vHC infusions of the anti-*Arc* ODN significantly down-regulated basal and sucrose-induced vHC *Arc* expression. Specifically, vHC *Arc* expression in the hemisphere injected with the scrambled control was higher in rats given access to sucrose than in rats given access to water ($t_{(3)} = 5.286$, $P = 0.0132$). In rats given access to water, vHC *Arc* expression was significantly lower in the hemisphere injected with the vHC anti-*Arc* ODN compared with the opposite hemisphere that was injected with the scrambled control ($t_{(3)} = 5.353$, $P = 0.0332$), and a similar effect was observed in rats that had consumed sucrose ($t_{(2)} = 14.11$, $P = 0.0050$).

Premeal inhibition of vHC NMDARs and down-regulation of vHC *Arc* does not affect licking speed

vHC infusions of APV and the anti-*Arc* ODN did not affect licking speed; that is, the number of licks per second did not differ between vehicle and APV conditions ($Z = -0.594$, $P = 0.552$) (Fig. 5A) nor between anti-*Arc* ODN and scrambled control conditions ($t_{(8)} = -0.755$, $P = 0.879$) (Fig. 5B).
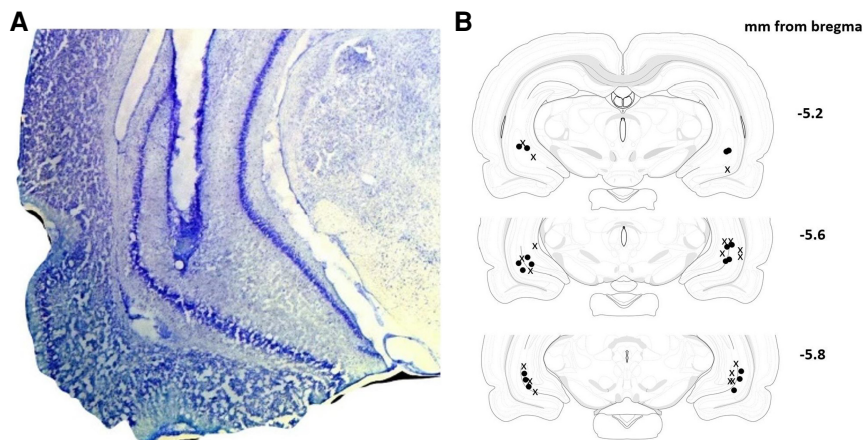

Figure 1. Cannula placement in vHC. (*A*) Representative depiction of a vHC injection site in thionin-stained tissue. (*B*) Schematic depiction of vHC cannulae placement relative to bregma. (X) APV injections, (filled black circle) anti-*Arc* ODN injections. Adapted from Swanson (2004).
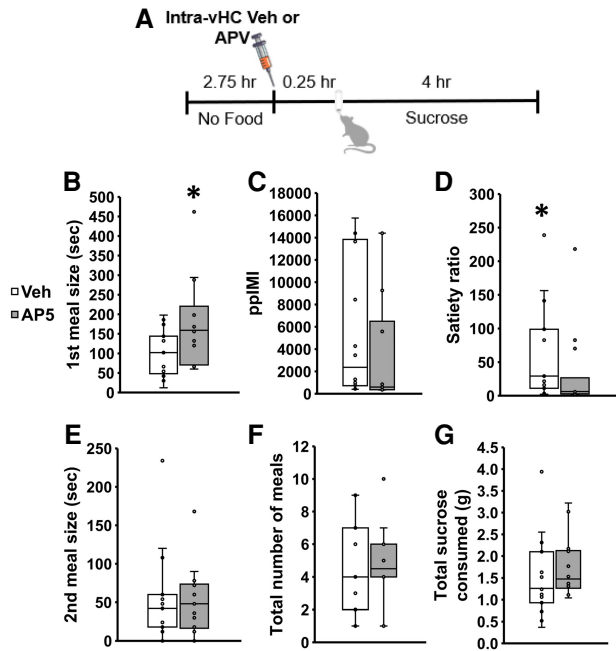
Figure 2. Premeal inhibition of vHC NMDARs increased the amount consumed during the first sucrose meal and disrupted the relationship between meal size and the timing and size of the next meal. (*A*,*B*) Compared with vehicle infusions, APV infusions (*n* = 13; within-subject) increased the size of the first meal that was consumed after the infusion. (*C*,*D*) Rats did not compensate for this increase by waiting longer to eat their next meal (*C*), resulting in a decreased satiety ratio (*D*). (*E*) Rats also did not compensate for the increased intake by eating a smaller second meal. (*F*,*G*) vHC APV infusions did not affect the total number of meals (*F*) or the total amount of sucrose (*G*) consumed during the 4-h experimental period. (*) *P* < 0.05 versus Veh.

Discussion

The current study is the first to show that blocking vHC NMDARs and *Arc* elevates energy intake by increasing meal size and promoting meal initiation, suggesting that vHC NMDARs and *Arc* inhibit feeding behavior. Specifically, we observed that inhibiting vHC NMDARs or vHC *Arc* increased the size of the first postinfusion meal and that the rats did not compensate by waiting longer to eat their next meal or by eating less during that second meal. Inhibiting vHC NMDARs or vHC *Arc* also significantly decreased the satiety ratio, which suggests that blocking these critical molecular steps needed for vHC synaptic plasticity decreased satiation (Zorrilla et al. 2005).

Given that synaptic plasticity and memory are the primary functions associated with vHC NMDARs and *Arc* (Inoue et al. 2005; Kouvaros and Papatheodoropoulos 2016; Papatheodoropoulos and Kouvaros 2016; Babiec et al. 2017; Zhang et al. 2017; Chiang et al. 2018; Hudgins and Otto 2019; Soler-Cedeno et al. 2019) and that pretraining vHC infusions of NMDAR antagonists and *Arc* ODNs impair memory (Czerniawski et al. 2011; Chia and Otto 2013), it is likely that blocking vHC NMDARs and *Arc* prior to ingestion increased energy intake by disrupting the molecular processes required for synaptic plasticity and memory formation. The possible role of memory is supported by findings showing that a variety of vHC manipulations affect food-related memory, such as cue-potentiated feeding (Kanoski et al. 2013), food-induced conditioned place preferences (Kanoski et al. 2011), and consolidation of the spatial location of food reinforcement (Kanoski et al. 2011). Moreover, we showed previously that optogenetic inactivation of vHC princi-

ple glutamatergic neurons given for 10 min immediately following the consumption of a chow, sucrose or saccharin meal, which is when the memory of the meal would presumably be undergoing consolidation, increases intake measured at a later time when vHC function has returned to baseline (Hannapel et al. 2019). vHC infusions of APV prevent learning-induced increases in vHC *Arc* suggesting that NMDARs and *Arc* are functionally coupled (Czerniawski et al. 2011; Chia and Otto 2013), which may explain why blocking NMDARs and *Arc* had a similar pattern of effects on energy intake in the present report.

Future research is needed to confirm whether memory is involved in vHC NMDAR and *Arc* control of intake and, if so, to identify the aspects of ingestion that are being remembered. For instance, blocking vHC NMDARs and *Arc* may have increased intake by impairing the memory of the satiating postingestive consequences of sucrose ingestion (Benoit et al. 2010). To address this, it would be informative to investigate whether blocking vHC NMDARs and *Arc* interferes with sensory-specific satiety and/or discrimination learning based on satiation states. Also, it would be important to determine whether these manipulations increase intake of the noncaloric sweetener saccharin, which has minimal postingestive consequences (Mook et al. 1980; Renwick 1985, 1986; Sclafani and Nissenbaum 1985; Foletto et al. 2016). Our finding that postmeal optogenetic inhibition of vHC glutamatergic neurons increases future saccharin intake suggests that postingestive consequences are not necessary for vHC glutamatergic neurons to influence energy intake because saccharin meal size is determined primarily by oropharyngeal processes rather than by postingestive consequences (Mook et al. 1980; Renwick 1985, 1986; Sclafani and Nissenbaum 1985; Foletto et al. 2016). It is also possible that blocking vHC NMDARs and *Arc* increased
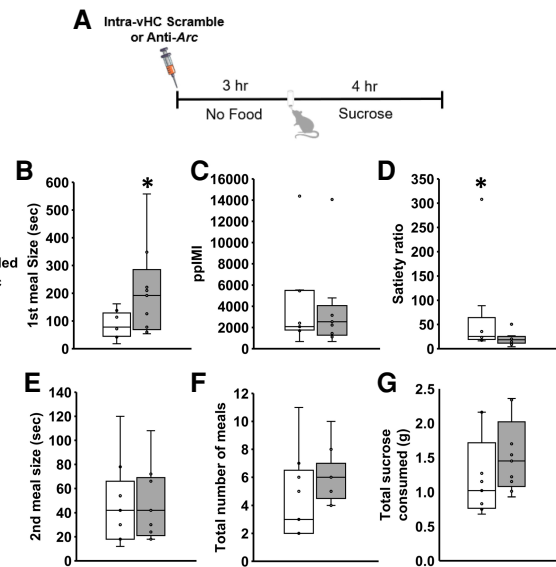

Figure 3. Premeal down-regulation of vHC *Arc* expression increased the amount consumed during the first sucrose meal and disrupted the relationship between meal size and the timing and size of the next meal. (*A*,*B*) Compared with scrambled vHC infusions, vHC infusions (*n* = 9; within-subject) of an Arc antisense ODN increased the size of the first meal that was consumed. (*C*,*D*) Rats did not compensate by waiting longer to eat the next sucrose meal (*C*), resulting in a decreased satiety ratio (*D*). (*E*) Rats also did not compensate by decreasing the amount the consumed during their second meal. (*F*,*G*) Down-regulating vHC Arc did not affect the total number of meals consumed (*F*), or the amount of sucrose consumed (*G*) during the 4-h experimental period. (*) *P* < 0.05 versus scrambled control.
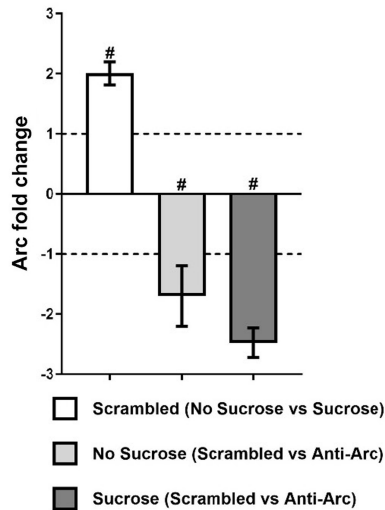
Figure 4. Sucrose consumption increases vHC *Arc* expression and vHC Arc antisense ODN infusions decrease vHC Arc expression. (*A*) Sucrose consumption increased vHC Arc expression in rats given the scrambled control (*n* = 4) compared with cage-control rats given water (*n* = 4; no sucrose). In rats given access to water, vHC Arc expression was significantly lower in the hemisphere injected with Arc antisense ODN (anti-Arc) than in the opposite hemisphere that was injected with the scrambled control (*n* = 4). A similar effect was observed in rats that had consumed sucrose. (#) *P* < 0.05 versus hypothetical value of 1 (i.e., no change in vHC Arc expression).

ingestion via mechanisms that do not involve memory, for instance by increasing food motivation (Kanoski et al. 2013; Hsu et al. 2015a, 2017; Yoshida et al. 2019), by disrupting the ability of hunger states to control synaptic plasticity as they do in the hypothalamus (Qi and Yang 2015), and/or by interfering with the ability of satiating signals such as leptin to suppress feeding via vHC neurons (Kanoski et al. 2011).

The findings in the present report are consistent with recent research showing that ingestion of palatable food increases neural activity in vHC glutamatergic neurons (Kosugi et al. 2021) and with our previous findings showing that vHC infusions of the GABA_A agonist muscimol (Hannapel et al. 2017) or optogenetic inhibition of vHC glutamatergic neurons (Hannapel et al. 2019) during the early postprandial period increases subsequent intake. The present results differ from our previous results in that the vHC muscimol infusions (Hannapel et al. 2017) and optogenetic inhibition (Hannapel et al. 2019) decreased the ppIMI duration and increased the amount consumed during the subsequent second meal. It is unclear why the APV and *Arc* antisense did not have a similar effect. Given that APV inhibits NMDAR function for at least 100 min (Morris 1989) and the *Arc* antisense inhibits *Arc* expression for hours (Guzowski 2002), it is likely that the APV and *Arc* antisense inhibition was still in effect during intake of the second meal. One likely reason for the differences is that muscimol and optogenetic inhibition of the glutamatergic neurons likely disrupt more molecular processes in vHC than does specific blockade of NMDARs or *Arc* expression. Another obvious difference between the present study and these previous ones is that rats in the current study were given infusions prior to the initial sucrose consumption rather than after the meal was completed. Perhaps the increased intake during the first meal in the present experiment activated satiety factors that compensated for the absence of hippocampal inhibition during intake of the second meal (Moran 2006; Cummings and Overduin 2007; Moran and Dailey 2011).

The present finding that blocking vHC NMDARs and *Arc* increases initial but not later consumption is in contrast to our previ-

ous results showing that inhibition of vHC glutamatergic neurons during intake does not affect the amount consumed during that meal (Hannapel et al. 2017) and with findings in humans showing that distraction while eating has a bigger effect on increasing intake at the next eating episode than on current intake (Robinson et al. 2013). The current findings are similar to observations in patient H.M. and others with memory deficits who would report not remembering having just eaten to satiation and would consume more food if offered, essentially extending the size of the meal during that sitting (Hebben et al. 1985; Rozin et al. 1998; Higgs 2008).

Several lines of evidence suggest that the increase in sucrose intake produced by vHC infusions of APV and the anti-*Arc* ODN were not likely due to a generalized increase in behavior. For instance, previous reports have shown that vHC infusions of APV either did not affect (Nascimento Hackl and Carobrez 2007; Motevasseli et al. 2010) or decreased locomotor activity (Rezvanfard et al. 2009) in an elevated plus maze. Similarly, the ability of vHC infusions of APV and the anti-*Arc* ODN to influence conditioned freezing are not due to generalized locomotor activity (Czerniawski et al. 2011; Chia and Otto 2013). Finally, the present results show that vHC infusions of APV and the anti-*Arc* ODN increased meal size without increasing licking speed.

Although sucrose has been used commonly in studies of energy intake, it will be important to determine in the future whether the present findings can be generalized to normal feeding with mixed macronutrients. It is likely that blocking vHC NMDARs and *Arc* will increase the intake of foods that include fats and proteins because we found previously that optogenetic inhibition of vHC glutamatergic neurons increases intake of standard chow and a 32% sucrose solution in a comparable manner (Hannapel et al. 2019). Also, vHC lesions (Davidson et al. 2009) and vHC infusions of the orexigenic hormone ghrelin (e.g., Kanoski et al. 2013; Suarez et al. 2020) increase chow intake.

In summary, the present findings indicate that impairing vHC NMDAR function or *Arc* expression increases meal size and disrupts the mechanisms that limit future intake. It will be essential to determine whether vHC NMDARs and *Arc* inhibit intake through a process that requires synaptic plasticity, memory, and/or motivational processes. These findings advance our understanding of the neural mechanisms that regulate energy homeostasis, which may facilitate the development of novel treatments for disorders that involve disrupted energy regulation, such as obesity.

Materials and Methods

Subjects

Adult male Sprague–Dawley rats (*n* = 31 postnatal days 52–58 upon arrival) (Charles River Laboratories) were single-housed in Optirat cages (Animal Care Systems). Unless otherwise stated, the rats
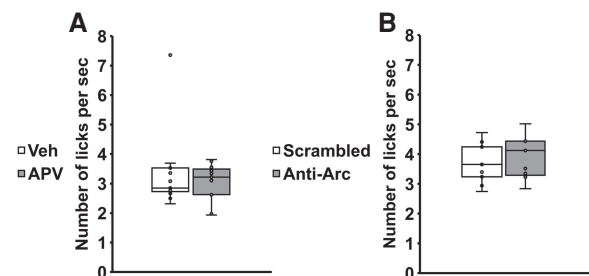

Figure 5. Intra-vHC infusions of APV and anti-*Arc* did not affect licking speed. (*A*,*B*) The number of licks per second did not differ between vHC vehicle and APV infusions (*n* = 13; within-subject) (*A*), or between vHC scrambled and Arc antisense ODN infusions (*B*) (*n* = 9; within-subject).

were kept on a 12:12 h light–dark cycle and given ad libitum access to pelleted food and water in their home cages. All procedures were performed in compliance with the National Institutes of Health guidelines for care of laboratory animals and approved by the Georgia State University Institutional Animal Care and Use Committee.

Stereotaxic surgery

At least 1 wk after arrival, the rats were anesthetized with 5% isoflurane (Henry Schein Impromed) in 1000 mL/min of oxygen (Airgas) and given penicillin (1500 IU, i.m.; Henry Schein Impromed) and carprofen (5 mg/kg, sc; Henry Schein Impromed). Anesthesia was maintained with 1%–3% isoflurane gas mixed in 500 mL/min oxygen for the duration of the surgery. Unilateral (experiment 1) or bilateral (experiment 2) guide cannulae (8.5 mm long, 26-gauge; Plastics One) were implanted aimed at the vHC (AP: −5.3 mm; ML: ±5.1 mm; DV: −6.4 mm from skull) (Paxinos and Watson 2007). We have found previously that unilateral vHC manipulations are sufficient to increase energy intake (Hannapel et al. 2017, 2019). The unilateral cannulae in experiment 1 were implanted in left or right vHC in a counterbalanced manner. Guide cannulae were held in place by jewelers' screws (Plastics One) and cranioplastic cement (DuraLay, Reliance Dental Mfg. Co.) and an obdurator (Plastics One) was inserted into the cannula. The rats were given sterile saline (0.9%; 3.00 cc, s.c.; Hospira) at the end of surgery and allowed to recover for at least 1 wk before behavioral training.

Sucrose exposure

Sucrose (32% [w/v] solution) was used to assess energy intake. This concentration is palatable and rewarding to rats and thus they typically consume it readily upon presentation (Hajnal et al. 2004; Smith 2004). Also, its stimulus qualities are more specific than meals that include fats and proteins, its postingestive consequence have been extensively characterized (Waldbillig and Bartness 1981; Kirkham and Cooper 1988; Davis et al. 2000) and it cannot be hoarded. Moreover, sucrose was used in the present experiment to permit comparisons with our previous findings showing that inhibition of vHC principal glutamatergic neurons increases sucrose intake and that sucrose consumption increases *Arc* expression in vHC glutamatergic neurons (Hannapel et al. 2017, 2019).

Rats were given access to sucrose at the same time and place for several days prior to the infusions in order to avoid any effects of novelty and to increase the likelihood that they would approach and consume the sucrose on the testing days. On the first exposure day, the rats were brought to the testing room at the beginning of the light cycle, placed into polycarbonate testing cages (22 cm × 43 cm × 22 cm) that did not contain any chow but did have water, and were then given the sucrose solution 8 h later for 10 min. Rats were exposed to sucrose in a similar manner on subsequent days with the exception that sucrose was presented 3 h after the rats were placed into the testing cages rather than 8 h later. We started with an 8-h period without chow in order to increase the likelihood that the rats would approach the bottle but then decreased it to 3 h to be within the range of an average postprandial intermeal interval (ppIMI) (Snowdon 1969). In experiment 1, 15 rats were initially exposed to the sucrose solution daily until they consumed the sucrose in <30 sec from initial presentation of the sucrose bottle for three consecutive days. The number of days that it took the rats to reach the criterion during the sucrose exposure period ranged from 6 to 12 d (M = 8; SEM = 2). Given that familiarity decreases the involvement of NMDARs in memory (Shapiro and O'Connor 1992; Caramanos and Shapiro 1994), we exposed an additional five rats to sucrose for only 3 d before the drug infusions in order to reduce familiarity with sucrose. The same procedure used during the first 3 d of sucrose exposure described above was used and aside from reducing the number of sucrose pre-exposure days, these five rats were treated in the same manner as the other 15 rats (see testing days and infusions). Importantly, our results indicated that the effects of APV did not differ between rats trained to a criterion versus those pre-exposed to sucrose for only 3 d and thus

these data were combined into one APV group. For experiment 2, the 16 rats were given 3 d of sucrose exposure because repeated experience in a learning task also diminishes learning-induced *Arc* expression (Kelly and Deadwyler 2002, 2003; Guzowski et al. 2006) and our findings suggest that increased familiarity with sucrose diminishes the ability of sucrose to increase dHC *Arc* expression (Henderson et al. 2016).

Testing days and infusions

Experiment 1

Testing days started 24 h after the last sucrose exposure day. The rats were placed in their experimental cages in the testing room without food for 2.75 h and then removed from the cage and given an intra-vHC infusion of 0.5 μL of vehicle (0.25 μL/min phosphate-buffered saline [PBS] at pH 7.4; Cellgro) or DL-APV (30 mM; Tocris). The injection needle extended 1.0 mm beyond the bottom of the guide cannula and was left in place for 2 min following the injection to facilitate diffusion. The rats were returned to the testing cage and given sucrose 15 min later for 4 h during which the size of sucrose meals, the interval between meals, and total consumption were recorded. This dose and timing of the APV injection were selected because this APV dose impairs memory when infused into the vHC prior to training (Bast et al. 2005; McHugh et al. 2008; Czerniawski et al. 2011, 2012) and because this is when the drug has its maximal effect on NMDA receptors (Rossato et al. 2018). A within-subject design was used wherein rats were given infusions of vehicle or APV in a counterbalanced order with 72 h between infusions.

After the completion of the behavioral tests, the rats were deeply anesthetized using 5% isoflurane gas (Henry Schein Impromed) in 1000 mL/min oxygen (Airgas, Inc.), decapitated and their brains removed and stored in formalin for at least 48 h. Brains were then sectioned (50 μm) and two observers that were blind to the behavioral results examined the sections to estimate the infusion location 1.0 mm below the bottom of the cannula tract.

Experiment 2

Twenty-four hours after the last sucrose exposure day, rats were given bilateral infusions (0.5 μL; 0.25 μL/min) of either an anti-*Arc* (2 nmol/μL) or scrambled ODN (Integrated DNA Technologies). The anti-*Arc* ODN targeted *Arc* mRNA bases 209–228 and was chosen based on effective knockdown of *Arc* mRNA and protein (Guzowski et al. 2000; Ploski et al. 2008; Czerniawski et al. 2011, 2012; Chia and Otto 2013). The scrambled ODN was composed of the same base composition in a randomized order. The anti-*Arc* ODN or scrambled control were given 3 h prior to sucrose exposure based on previous studies showing that the anti-*Arc* impaired learning and memory tested 3 h after infusion (Guzowski et al. 2000; Czerniawski et al. 2011; Chia and Otto 2013). The rats were given both the anti-*Arc* or scrambled control with 72 h between injections in a counterbalanced manner.

Twenty-four hours after the last sucrose testing day, the rats were given the scrambled control in one hemisphere and the anti-*Arc* in the other and then given access to water or sucrose for 10 min 3 h later. Hemispheres were counterbalanced between animals. Fifteen minutes later the rats were euthanized with a lethal dose of pentobarbital (120 mg/kg; Henry Schein Impromed) and perfused transcardially. The brains were sectioned and examined for cannulae placement as in experiment 1 and bilateral vHC tissue punches (0.5 mm; Leica Biosystems) were also taken and processed for qRT-PCR.

Data acquisition

All intake data were recorded using a modified lickometer system that measured the change in system resistance when a rat licked from a sipper tube (Lafayette Instruments model 86062). The Activity Wheel Monitoring Program (Lafayette Instruments) recorded all sipper tube contacts. A meal was defined as any bout

containing at least 30 licks (Smith 2000; Hannapel et al. 2017). All sipper tube contacts were assumed to result in ingestion and the amount consumed was estimated indirectly by summing the duration of all sipper tube contacts during the meal. The end of a meal was operationally defined as five consecutive minutes without any sipper tube contact. This criterion was used because after five consecutive min without consumption, there is a low probability that rats will initiate eating again (Zorrilla et al. 2005; Fekete et al. 2007) and an increased probability that they will groom, sniff, rear and rest, which is known as the behavioral satiety sequence (Antin et al. 1975; Thaw et al. 1998; Zorrilla et al. 2005).

Meal size was estimated by measuring the total amount of time spent in contact with the sipper tube during the meal, which excluded time spent not licking. Rats that did not consume more than one meal were given a maximum ppIMI of 4 h (i.e. the duration of the recording period). Larger meals lead to a longer duration until the next meal, which is known as the postprandial correlation (Le Magnen and Tallon 1963). The satiety ratio (ppIMI/size of preceding meal) was also calculated because it controls for the effects of variations in the size of the first meal on the duration of the subsequent ppIMI. The satiety ratio is an index of the amount of time spent not eating that is produced by the previous meal (Panksepp 1973; Zorrilla et al. 2005). It was calculated in the present experiment by dividing the interval between the first and second meal by the size of the first meal in seconds. Total sucrose intake was estimated by weighing the bottle before and at the end of the experimental session. Licks per second were calculated by dividing the total number of licks by meal size in seconds.

Quantitative real-time PCR (qRT-PCR)

RNA was isolated and purified using mirCURY RNA isolation kit (Exiqon). RNA concentrations were determined using a NanoDrop-2000 spectrophotometer (Thermo Fisher Scientific ND-2000). Total RNA was reverse transcribed using Transcriptor first stand cDNA synthesis kit (Roche) and stored at −20°C overnight. qRT-PCR was performed with commercially available primers for *Arc* (Qiagen PPR44661A-200) and for the reference gene GAPDH (Qiagen PPR06557B-200) using a FastStart essential DNA green master mix (Roche). Samples were run in duplicate per gene in a LightCycler 96 instrument (Roche). The samples were preincubated for 10 min at 95°C and run through 55 cycles of three-step amplification consisting of 10 sec at 95°C, 10 sec at 60°C, and then 10 sec at 72°C. Relative quantification of *Arc* was determined using the Pfaffl method (Livak and Schmittgen 2001).

Statistical analyses

All statistical analyses and graphs were generated using IBM SPSS Statistics for Windows (IBM Corporation) and Excel (Microsoft Corporation). The behavioral data were tested for normality using Shapiro–Wilk tests and homogeneity of variance using Bartlett's tests and the following measures were not normally distributed: all APV data except total meals consumed and the satiety ratio, ppIMI, and total number of meals consumed for the anti-*Arc* experiment. Therefore, these data were analyzed using the nonparametric Wilcoxon signed-rank tests. Paired *t*-tests were used to compare the remaining measures. qRT-PCR data were first compared with a hypothetical value of 1 (i.e., no change in *Arc* expression) and then a one-way ANOVA was performed to examine group differences with Bonferroni multiple comparison post hoc tests.

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