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Memory and eating: A bidirectional relationship implicated in obesity

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Abstract

This paper reviews evidence demonstrating a bidirectional relationship between memory and eating in humans and rodents. In humans, amnesia is associated with impaired processing of hunger and satiety cues, disrupted memory of recent meals, and overconsumption. In healthy participants, meal-related memory limits subsequent ingestive behavior and obesity is associated with impaired memory and disturbances in the hippocampus. Evidence from rodents suggests that dorsal hippocampal neural activity contributes to the ability of meal-related memory to control future intake, that endocrine and neuropeptide systems act in the ventral hippocampus to provide cues regarding energy status and regulate learned aspects of eating, and that consumption of hypercaloric diets and obesity disrupt these processes. Collectively, this evidence indicates that diet-induced obesity may be caused and/or maintained, at least in part, by a vicious cycle wherein excess intake disrupts hippocampal functioning, which further increases intake. This perspective may advance our understanding of how the brain controls eating, the neural mechanisms that contribute to eating-related disorders, and identify how to treat diet-induced obesity.

Key words: amnesia, appetite, cognition, diet, episodic memory, food intake, hippocampus, interoception

1. INTRODUCTION

To date, the scientific effort to understand how the brain controls eating has focused primarily on brain areas involved in hunger, fullness and pleasure. In contrast, a critical question in behavioral neuroscience that has been relatively poorly addressed is how top-down cognitive processes such as memory modulate energy intake. Evidence suggests that hippocampal-dependent episodic memory of recent eating (i.e., autobiographical memories of personal experiences that have "what", "when", and "where" components) inhibit subsequent eating behavior. Episodic memories of personal experiences can last for hours, days, weeks and years, whereas physiological signals generated by ingestion typically last for many hours (Shimy et al., 2020). As a result, memory of a recently eaten meal can serve as a powerful mechanism for controlling future eating behavior because it provides a record of recent intake that likely outlasts most physiological signals generated by a meal. Moreover, episodic memories can provide more detailed information about what, where and what has been eaten than can these physiological signals. The brain has evolved many mechanisms to promote food-seeking and consummatory behaviors; however, neural controls are also needed to inhibit these behaviors, for instance, when sufficient energy has been obtained, to avoid predation, and to promote reproduction. Factoring in memory of recent energy intake into decisions about when, what and how much to eat during the next eating episode promotes flexibility and allows animals to avoid aversive physiological effects of overconsumption or costs associated with unnecessary foraging. Using memory for recent eating to control future eating is also advantageous because prior knowledge about the physiological consequences of foods on the body can be taken into account.

Moreover, being able to integrate physiological signals with memory of the meal may allow for improved prediction of the consequences of future consumption. This raises a critical question regarding how cues associated with energy status (e.g., ghrelin, leptin) interact with neural mechanisms involved in memory to control eating. These questions are important given evidence reviewed below suggesting that impaired hippocampal-dependent function causes overeating and weight gain and thus may contribute to the development and maintenance of obesity. Knowing how cognitive processes such as memory control intake will provide a more complete understanding of how the brain controls eating and will likely provide insights regarding the brain mechanisms that contribute to eating-related disorders, such as diet-induced obesity.

This paper will review evidence from human research showing that amnesia is associated with impaired processing of hunger and satiety cues, disrupted memory of recent meals, and overconsumption, and that meal-related memory influences decisions we make about what and how much to eat. Then, evidence from rodents suggesting that neural activity and synaptic plasticity in hippocampal neurons is critical during the postprandial period for limiting future intake will be reviewed, as well as findings showing that endocrine and neuropeptide systems act in the hippocampus to regulate learned aspects of eating. Finally, the ways in which overeating and obesity impair memory and hippocampal function in humans and rodents will be described. Throughout, we attempt to identify gaps in our understanding and future directions. Collectively, this review will present evidence that is consistent with the possibility that diet-induced obesity is caused and/or maintained, at

least in part, by a vicious cycle wherein excess intake disrupts the functioning of brain areas critical for memory, which further increases intake (Clasen et al., 2020).

2. IMPACT OF LEARNING AND MEMORY ON INGESTION IN HUMANS

2.1. Evidence from neuropsychological studies

The first clues that memory for recent eating might be important in human appetite control came from observations of patients with amnesia. These patients, who are unable to remember what they have eaten, appear to have disturbances in appetite (Hebben et al., 1985; Higgs, Williamson, & Attwood, 2008; Rozin et al., 1998). Hebben and colleagues (1985) first noted that the famous amnesic patient H.M., who suffered memory loss following brain surgery to treat his epilepsy, hardly ever mentioned being hungry or thirsty, even when he had not eaten or drank anything for some time (Hebben, et al. 1985). To investigate whether his appreciation of internal states had been affected by the surgery, the researchers asked H.M. to rate his hunger and thirst on several occasions before and after eating. H.M. often reported feeling neither hungry nor full, even when he had just completed a meal. Indeed, on some occasions, he reported feeling less full *after* a meal than before. A "dinner" experiment was also conducted in which H.M. was offered a large amount of food to see if overconsumption might shift his appetite ratings. One evening, after he had finished his usual dinner, any evidence of that meal was removed, and within 1 minute, a second, identical meal was offered. H.M consumed all of the first meal and then went on to eat most of the second meal, but even so, his appetite ratings still did not approach satiety. When questioned 20 minutes later, he could not remember having eaten anything. In the same study, other patients with global amnesia were similarly asked to rate

their appetite. In contrast to H.M., three out of four of these patients reported expected decreases in hunger and thirst after all meals. Based on this evidence, Hebben and colleagues (1985) concluded that because most of the other patients with global amnesia reported normal appetite, the disturbances exhibited by H.M. were unlikely to be attributed to his memory loss. However, the results of further neuropsychological studies have suggested that impaired memory is associated with a deficit in satiety. For example, Rozin and colleagues (1998) found that two profoundly amnesic patients ate multiple meals one after another as they were offered: one of the patients consumed two 3-course meals before rejecting an additional meal (Rozin et al., 1998). The explanation forwarded by the authors was that intake is usually constrained by a social norm that eating should stop after a meal has been consumed and because the amnesic patients cannot remember having just eaten, they eat beyond the bounds of what is considered “normal consumption”.

Higgs and colleagues reported similar multiple meal consumption by two amnesic patients and provided evidence that this is a specific effect because other aspects of eating were unaffected (Higgs, Williamson, Rotshtein, et al., 2008). Specifically, sensory-specific satiety (the decline in the pleasantness of food as it is eaten) was intact in these patients and they also responded similarly to control participants when asked to rate the pleasantness of yogurts that had increasing amounts of sugar added, suggesting that their appreciation of sweet taste was normal. The authors reasoned that amnesic patients may consume multiple meals because they are unable to use information about recent consumption encoded in memory to inhibit further consumption. However, as with any studies of neuropsychological patients, the results of these investigations remain open to

interpretation: the patients had suffered damage to areas of the brain associated with memory (e.g., hippocampus) but also to other areas involved in emotional responding (e.g., amygdala and orbitofrontal cortex) and had a range of neuropsychological problems. Therefore, an important next step in investigating the involvement of memory for recent eating in appetite in humans was to conduct experimental studies of healthy volunteers.

2.2. Manipulating meal memories in healthy volunteers

2.2.1. *Recall of the most recent eating episode*

A series of experiments by Higgs and colleagues were the first to investigate the effects of recall of recent eating on subsequent intake in healthy volunteers (Higgs, 2002; Higgs, Williamson, & Attwood, 2008). The rationale behind these studies was that if memory for recent eating inhibits intake, then boosting such memories by asking participants to recall a recent meal should enhance this effect. In the first study, participants ate a pizza lunch in the laboratory and then returned 3 hours later to take part in a snack taste test (Higgs, 2002). Just before the taste test, participants were randomly allocated to either the experimental condition, in which they were asked to write down their thoughts on the lunch they had eaten earlier, or to a control condition in which they were asked to write down thoughts about anything they wished. All participants had consumed the same fixed amount of pizza at the lunch and so the only difference between the conditions was whether they were asked to recall that lunch. Immediately after completing the recall task, the participants were invited to taste and rate some cookies and intake of the cookies was covertly measured. The lunch recall group ate significantly fewer cookies than the control group. These results are consistent with the suggestion that

memory of the most recent meal has an inhibitory effect on subsequent intake, but they do not provide evidence of specificity for the recall of that particular meal: it is possible that thinking about any eaten food would have had the same effect. To address this issue, a follow-up study was conducted that included an additional control group in which the participants were asked to recall lunch they had eaten the *previous* day (Higgs, 2002). This condition controlled for general demand characteristics associated with meal recall and provided a test of whether the effect is specific to recall of the most recently eaten meal. Intake of cookies in the two control groups did not differ, but the inhibitory effect of recalling lunch eaten that day on later intake was replicated.

To further explore the specific role of memory-related processes in the effect of meal recall, another study was conducted that used the same recall paradigm but varied the time between consumption of the lunch and the recall session (Higgs, Williamson, & Attwood, 2008). The rationale here was that if the effect of recalling the most recent meal is reliant on memory processes, no effect of recall would be expected soon after the lunch, because at that point the memory of the meal would still be strong and so additional recall would have little effect. On the other hand, if the effect is due to non-memory related processes, such as meal recall inducing guilt about the lunch that was eaten, then the effects of recall would be expected to be similar regardless of the delay. Participants were either allocated to a “lunch today” recall group or a “lunch yesterday” recall group. For each group, on one test day the recall session and taste test occurred 1 hour after lunch had been eaten and on the other test day the cookie taste test occurred 3 hours after lunch. Participants who recalled the lunch eaten that day 3 hours after lunch, but not 1 hour after

lunch, ate fewer cookies at the taste test than did the participants who recalled lunch eaten the previous day. The delay-dependency of the effect is supportive of a memory-related explanation of the phenomenon. Nevertheless, participants in this and other meal recall studies were consuming cookies at the taste test and so it is possible that participants may have reduced their intake at the taste test when reminded of recent eating because the reminder triggered thoughts about dieting and limiting intake of high calorie food. However, this explanation seems unlikely because it has been reported that recall of recent eating also reduces intake of low-calorie plain popcorn and reduces the intake of both restrained and unrestrained eaters (Higgs, Williamson, & Attwood, 2008). Furthermore, the effect is not dependent upon the type of lunch that is recalled, because the inhibitory effect of meal recall is observed regardless of whether participants consume a fixed lunch in the laboratory or whether they eat a self-selected lunch in their usual environment (Higgs, 2002; Higgs, Williamson, & Attwood, 2008). Because the effect is not restricted to thinking about consumption of specific food(s) (e.g., pizza), it is unlikely to be underpinned by mechanisms related to consumption of what may be regarded as unhealthy or forbidden foods.

The inhibitory effect of recalling recent eating on subsequent consumption has now been replicated many times by several research groups and some of the boundary conditions have begun to be investigated and the underlying mechanisms further investigated. Three additional studies found that recall of lunch eaten earlier reduces subsequent consumption (Collins & Stafford, 2015; Szypula et al., 2020; Vartanian et al., 2016) and one study found that recall of a recently consumed beverage inhibited lunch

consumption (Yeomans et al., 2017). Across all recall studies (including the earlier studies by Higgs and colleagues) no consistent effects have emerged of meal recall on either appetite or mood ratings, suggesting that changes in these variables do not underlie the decreased intake. It also appears unlikely that meal recall suppresses intake by enhancing general health consciousness, because recall of a recent exercise bout (which might reasonably be expected to cue health-related thoughts) does not affect subsequent snack intake (Vartanian et al., 2016).

Work by Szypula and colleagues (2020) has further extended knowledge about the effects of meal recall by highlighting the importance of moderating contextual factors. These authors replicated the inhibitory effect of meal recall on snack intake, but only when participants freely recalled the lunch and wrote these thoughts down (as in the original studies by Higgs and colleagues). When a guided recall procedure was used, no effect on intake was observed; in fact, the participants tended to eat more following the guided recall (Szypula et al., 2020). The reason for this finding is not clear but may be related to the specific nature of what is recalled. The guided recall procedure used by Szypula and colleagues (2020) focused on sensory/hedonic aspects of the meal, which could have shifted focus away from remembering the consumption episode to thinking about food more generally. In line with this idea, it has been found that exposure to food cues *per se* tends to increase rather than decrease consumption (Fedoroff et al., 1997). Future studies could investigate whether guided recall focused on food consumption, such as the associated bodily sensations, decreases subsequent intake. Szypula and colleagues (2020) also found no effect on intake when participants recalled the meal verbally in the presence

of the experimenter. Again, it is unclear why this was the case, but (Collins & Stafford, 2015) observed that the inhibitory effect of meal recall was attenuated when participants engaged in a positive mood induction task immediately after recall. It is possible that distraction away from the meal recall either by verbal interaction with the experimenter or positive mood induction reduces the effectiveness of the recall on subsequent consumption.

In summary, recall of the most recent eating episode has been found to inhibit subsequent consumption and this effect appears to be robust. Data from these meal recall studies support the idea that information in memory about the last meal is factored into decisions about subsequent consumption. However, evidence from one paradigm is inevitably limited by specific aspects of that method. In the case of the meal recall paradigm, participants are explicitly asked to think about what they have recently eaten and so it remains possible that non-memory related consequences of this procedure underlie, at least in part, the inhibition of intake. Therefore, it is important to test the effects of different kinds of meal memory manipulations to examine generalizability of the results.

2.2.2. *Disrupting meal memory encoding*

An alternative approach to testing the idea that memory for recent eating inhibits later intake is to focus on encoding of the meal memory rather than on explicit recall. If memory for recent eating is important in appetite control, then manipulations that either impair or enhance the formation of meal memories at the time of consumption should

affect later intake. One way meal memory encoding can be disrupted experimentally is to divert participants' attention away from the food being consumed by asking them to engage in as secondary activity such as watching TV or playing a computer game while eating. Several studies have employed such a paradigm, and all have found that dividing attention between the meal and the secondary activity results in a poorer meal memory and greater snack intake at a later taste test (Higgs & Woodward, 2009; Mittal et al., 2011; Oldham-Cooper et al., 2011). For example, Higgs and Woodward (2009) found that participants who consumed their lunch while watching television ate more cookies at an afternoon tasting session than did participants who ate exactly the same lunch but without the television distraction. The participants who had the television lunch also rated their meal memory as much less vivid that then control participants. A similar study by Brunstrom and colleagues (Oldham-Cooper et al., 2011) found that playing a computer game while eating lunch was associated with greater afternoon snack intake and less accurate recall of the order in which they ate different food items at lunch.

This ability of distraction during eating to increase later intake has been found regardless of the whether participants watched a boring, sad or funny television program, suggesting that the effect cannot be easily explained by an effect of the distracting activity on mood (Mittal et al., 2011). One recent study found no relationship between meal memory and later snacking, but in this study (unlike in previous studies) participants were also able to consume more when distracted because the amount of food eaten was not controlled and so this complicates interpretation of the results (Francis et al., 2017). Two studies have manipulated the *level* of distraction during consumption and assessed effects

on subsequent intake. In the first study, the level of engagement with a concurrent computer task was manipulated using a financial incentive: in one condition participants were rewarded with a small amount of money if they played the game well (high engagement condition) and in another comparable condition no financial was offered (low engagement condition). Both distraction conditions were compared with a "no computer playing" control condition. Recall for the serial order of lunch items and memory vividness of the lunch was reduced and subsequent consumption was greater in the high engagement compared to the control condition with the low engagement condition in between (Higgs, 2015). In the second study, participants were distracted by engaging in either a low or high perceptual load task while consuming a either a high or low calorie preload drink that was delivered directly into the mouth via an intra-oral infusion device (Morris et al., 2020). In the low perceptual load condition, ingestion of the high-calorie drink increased rated satiety and reduced consumption at a subsequent snack test, but in the high perceptual load condition participants did not reduce their satiety or intake after the high calorie load, suggesting that greater attentional load during consumption impaired later satiety responses. There was no effect of the attentional manipulation on memory for preload sensory characteristics (how creamy, sweet, and pleasant it was) and so further studies are required to assess the precise mechanisms underlying the effects of the attentional manipulation on satiety in this paradigm.

2.2.3. *Enhancing meal memory encoding*

The effect of enhancing meal memory encoding has been investigated across several studies but the picture that has emerged here is not clear. Four initial studies used a

paradigm in which participants were directed to pay more attention to food as it is eaten with the idea that this should facilitate meal memory encoding and reduce later food intake (Higgs, 2015; Higgs & Donohoe, 2011; Robinson et al., 2014; Seguias & Tapper, 2018). Focusing on the sensory characteristics of food while eating (sometimes referred to as "mindful" or "attentive eating") was associated with reduced intake at the next episode, but there was no clear evidence from these studies that the effect was related to enhanced memory of the previous eating episode. More recent investigations have found no effect of focusing on food as it is eaten on either subsequent consumption or meal memory (Tapper & Seguias, 2020; Whitelock, Gaglione, et al., 2019; Whitelock et al., 2018; Whitelock & Robinson, 2018).

Another study took a slightly different approach and attempted to enhance meal memory by asking participants to rehearse what was satisfying about the meal immediately after consumption and this study also failed to show an effect on memory or intake (Whitelock & Robinson, 2018). Two further studies manipulated the amount of oral processing of food as a means of enhancing attention to and sensory processing of food as it is eaten (Higgs & Jones, 2013; Hinton et al., 2020). Higgs and Jones reported that prolonged chewing of food at lunch led to reduced later snacking but was not related to remembered vividness of the meal (Higgs & Jones, 2013). Hinton and colleagues found that a slower eating rate increased rated fullness during the inter-meal interval and resulted in participants recalling that they ate a larger portion than did participants who ate at a faster eating rate, but there was no effect of lunch eating rate on subsequent snack intake (Hinton

et al., 2020). Taken together, the data do not provide support for a clear relationship between slower eating, meal memory, and satiety.

The evidence that distraction during eating increases later intake and impairs meal memory appears robust, but the evidence that eating more "mindfully" decreases later intake and increases memory is not consistent. One reason for this might be that it is difficult to enhance memory for recently eaten food at the time of encoding due to ceiling effects. It has been argued that memory for eating may be more accurately remembered than other kinds of memories because of the importance of eating for survival (Seitz, Blaisdell, Polack, et al., 2019). In support of this idea, participants were much better at remembering the number of times they ate a candy than they were at remembering the number of times they placed a candy or a non-food object from a bowl to a another container (Seitz et al., 2021). Therefore, it may be easier to demonstrate that distracting participants during eating worsens memory of eating and leads to greater consumption than it is to demonstrate that enhancing memory of eating reduces later intake. Rather than attempting to enhance encoding, a more effective approach to studying the influence of episodic memory on later appetite might be to induce a false memory of intake. Brunstrom and colleagues developed a novel paradigm that created a mismatch between what participants actually ate and what they perceived they ate using a refilling soup bowl (Brunstrom et al., 2012). This set up dissociated the independent effects of episodic memory and gastric feedback on appetite: participants in one condition ate 300 ml of soup but were led to believe that they had consumed 500 ml of soup. Immediately after eating, hunger ratings were related to the physical amount that had been consumed, but later in

the post meal period hunger was predicted by the remembered rather than the actual portion size. The effect of altering memory in this way on later food intake has yet to be investigated, but there is potential to use this approach to further investigate the episodic food memory in appetite.

2.3. Future directions

An important overriding question in relation to the role of memory for recent eating in appetite that has yet to be answered relates to the type of memory that is involved. Research to date suggests that the memory is specific to aspects of the most recent meal, which points to the importance of episodic-like memory. Episodic memories contain contextual information about an experienced event, such as what happened, and where and when it happened (Clayton & Dickinson, 1998). It is unclear at present what aspects of the most recent eating event that are encoded are used to inform later decisions about eating. Evidence from of the lack of effectiveness of guided recall of the taste and texture of the food, where it was eaten and with whom (Szypula et al., 2020) suggests that these elements may less of a role than knowledge of the satiating effects of the food and how much of it was consumed. There is some evidence that higher calorie foods are remembered better than lower calorie foods but this does not extend to better memory for the context in which those foods were consumed (Seitz, Blaisdell, & Tomiyama, 2019). Further work could be directed at guiding recall to specific aspects of the consumption experience such as the internal sensations felt by the participants.

The methods that have been used to assess accuracy or quality of memory for recent eating will need to be refined to provide a more definitive test of whether the

experimental manipulations aimed at altering meal memory indeed do so and the extent to which any effects on appetite are mediated by memory processes. Many different measures have been used to date, including asking participants to rate the vividness of their memory, recall of the number of and serial order of items consumed, the number of episodic details, and remembered portion size. A few studies have tested whether meal memory manipulations affect later intake *because* they impair or enhance episodic memory for the meal (i.e., have tested for mediation effects), but the results have not been consistent. It is possible that these measures do not tap into the aspects of memory that are affected by meal memory manipulation and that underlie the effects on subsequent consumption. For example, if memory for internal sensation is important, then it would be necessary to measure more directly how accurately or vividly participants recall these sensations. Future studies should test for mediation effects and employ a range of measures to assess different aspects of meal memory.

Little is currently known about how individual differences play into the effects of memory for recent eating on appetite. Many of the studies to date have recruited homogenous populations such as women low in dietary restraint and inhibition, although both men and women have been found to reduce snacking after meal recall (Higgs, Williamson, & Attwood, 2008). Higgs and colleagues reported that participants who score high on a measure of dietary disinhibition (uncontrolled eating) did not reduce intake after meal recall (Higgs, Williamson, & Attwood, 2008), but Szypula and colleagues found that the inhibitory effect of meal recall on snack intake was not moderated by either dietary restraint or disinhibition (Szypula et al., 2020). They also found episodic memory ability was

not a moderator of the meal recall effect, but the memory task that was used to categorize participants as high or low in memory ability may not have measured differences in the kind of memory that modulates the meal-recall effect. Studies with larger more diverse samples are required to confirm whether meal recall suppresses eating regardless of individual differences in memory ability, eating behavior traits and sex.

2.4 Interim Summary

- There is converging evidence from studies using a range of methodological approaches that memory for recent eating plays a role in human appetite.
- Studies of amnesic patients have shown that being unable to remember a recent eating episode is associated with overeating.
- Experimental studies in healthy volunteers have found that impairing meal memory formation (e.g., via distraction during eating) is associated with increased later food intake whereas enhancing memory for recent eating (e.g., by recalling the most recent eating episode) decreases subsequent intake.

3. DORSAL HIPPOCAMPAL NEURONS LIKELY MEDIATE THE INHIBITORY EFFECTS OF MEAL-RELATED MEMORY ON FUTURE EATING BEHAVIOR IN RODENTS

It is well established that the hippocampus plays a pivotal role in memory in primates and rodents (Murray et al., 2018). In rodents, the hippocampus can be divided along the septo-temporal plane into dorsal (dHC) and ventral (vHC) regions (in primates

posterior and anterior, respectively). 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 (Barkus et al., 2010; Bienkowski et al., 2018; Dong et al., 2009; Fanselow & Dong, 2010; Moser & Moser, 1998; Strange et al., 2014; Thompson et al., 2008). dHC appears to be primarily responsible for the cognitive functions associated with the hippocampus, namely spatial and episodic-like memories (Barbosa et al., 2012; Drieskens et al., 2017; Hunsaker et al., 2008; Panoz-Brown et al., 2018; Zhou et al., 2012). Decades of research using food-motivated tasks has shown that manipulations that interfere with dHC function impair food-related memory, such as the location of food sources (Layfield et al., 2020), the conditions under which food will be available (Crystal et al., 2013) and when food is expected to arrive (Tam et al., 2015).

Given the critical role of dHC in mediating episodic memories, including those involving food, research conducted by the Parent group has focused on testing the hypothesis that dHC neurons mediate the inhibitory effects of ingestion-related memory on future intake observed in humans (Reviewed in Section 2.2). The strategy used to test this hypothesis has been influenced substantially by an extensive body of research showing that manipulations given immediately after a learning event target the consolidation of the memory of that event. This evidence indicates that memory traces are initially labile and gain stability and permanence through consolidation, and that peripheral or central treatments given immediately after learning can enhance or impair the consolidation of the memory of that event (Izquierdo & McGaugh, 2000; McGaugh, 2000). Several studies have used posttraining manipulations to show that dHC neurons are involved in memory

consolidation. Specifically, temporary disruption of dHC function during the period immediately following learning impairs retention performance when memory is tested later after the effects of the manipulations have worn off (Bonini et al., 2003; Jerusalinsky et al., 1992).

3.1. Postmeal dHC inhibition increases future intake

Inspired by the impact of posttraining interventions on memory consolidation, Parent and colleagues determined whether *postmeal* inhibition of dHC neurons, which would be expected to impair the consolidation of the memory of that meal, would increase subsequent intake. Initially, they tested the effects of dHC infusions of the $GABA_A$ agonist muscimol on eating behavior because dHC muscimol infusions reversibly hyperpolarize principal glutamatergic neurons (Majchrzak & Di Scala, 2000; Rombo et al., 2016) that play a central role in dHC-dependent memory (Baker & Kim, 2002; Izquierdo et al., 2008; Morris, 2013; Zamorano et al., 2018). Importantly, previous research has shown that posttraining dHC infusions of muscimol impair future retention performance, indicating that dHC is critical for the consolidation of the memory of that experience (Izquierdo et al., 1992; Oliveira et al., 2010). In support of a memory consolidation hypothesis, intra-dHC infusions of muscimol administered immediately following the end of a sucrose meal accelerates the initiation of the next meal, doubles the amount rats consume during that second meal, and increases the number of meals ingested during the period following the injection (Henderson et al., 2013).

This novel use of a postmeal treatment appears to be the first to show that dHC neurons inhibit future energy intake and suggests that dHC glutamatergic neurons are

critical, although the effects of muscimol could include dHC interneurons that also express $GABA_A$ receptors (Glykys et al., 2007; Mann & Mody, 2010; Semyanov et al., 2003). An additional limitation of these results is that muscimol inhibits neural activity for several hours (Majchrzak & Di Scala, 2000; Martin, 1991; Martin & Ghez, 1999). Thus, it is not clear whether these postmeal manipulations increase intake by disrupting memory-based processes during the early postprandial period versus effects on dHC function during consumption of the second and subsequent sucrose meals. To resolve this, Parent and colleagues used an activity-guided optogenetic approach that permits neural inhibition with remarkable temporal precision and used a construct containing a calmodulin-dependent protein kinase II (CaMKII)α promoter that limits opsin expression to glutamatergic neurons while sparing inhibitory neurons, fibers of passage, and glia (Butler et al., 2016; Han & Boyden, 2007; Kohl et al., 2011; Stark et al., 2013; Stark et al., 2014; Weitz et al., 2015; Yizhar et al., 2011). They first confirmed that optogenetic inhibition of dHC glutamatergic neurons for 10 min inhibits neuronal firing in a temporally specific and steady manner, and critically, that neuronal activity returns immediately to baseline as soon as the photoinhibition is terminated (Hannapel et al., 2019). These temporal and anatomical features permitted the specific inhibition of dHC glutamatergic neurons for 10 min that was restricted to the period either before, during or after ingestion, and importantly, allowed for the measurement of ingestive behavior at a later time when the neurons were no longer inhibited. As in the case of the muscimol infusions, photoinhibition given for 10 min after the end of a sucrose or chow meal promoted the initiation of the next meal and augmented the amount consumed during the next meal when the neurons were no longer inhibited

(Hannapel et al., 2019). The specificity of this effect was illustrated by the finding that inhibition given before or during the first meal did not affect the amount consumed during the first meal or the next one. The finding that inhibition given during intake did not affect the amount eaten during that meal is reminiscent of the findings in humans showing that disrupting episodic meal-related memory has a bigger effect on intake during the next eating episode than on intake of the meal being remembered (Robinson, Aveyard, et al., 2013).

An important characteristic of the effects of posttraining manipulations on memory is that the effects are time-dependent, such that the efficacy of posttraining treatments diminishes as the learning-treatment interval increases (McGaugh, 1966; McGaugh & Izquierdo, 2000). The period in which posttraining manipulations effectively influence future retention performance delineates the consolidation window for that particular experience. For example, temporarily inactivating dHC with tetrodotoxin (TTX) immediately after inhibitory avoidance training impairs memory tested 48 hours after acquisition; in contrast, dHC infusions of TTX given 6 hours after training have no effect (Lorenzini et al., 1996). Similarly, blocking dHC AMPA, NMDA, or metabotropic glutamate receptors after learning impairs retention in a time-dependent manner (Bonini et al., 2003; Jerusalinsky et al., 1992). To test the hypothesis that dHC neurons influence future intake through a process that requires meal-related memory consolidation, Parent and colleagues determined whether the effects of postmeal dHC photoinhibition are also time-dependent. Importantly, they showed that inactivation given 5 minutes after the end of a meal increases the amount

consumed during the next bout, whereas inactivation given 80 minutes later does not impact subsequent intake (Briggs et al., 2021).

Thus, like posttraining manipulations, the effects of postmeal manipulations on future intake are time-dependent, which is consistent with the hypothesis that postmeal manipulations disrupt the consolidation of the memory of the meal. An alternative interpretation is that the early postprandial period is crucial because of the timing of interoceptive visceral satiety cues generated by the meal (Page et al., 2012; Waise et al., 2018). This is possible given that disturbances in hippocampal function impair the sensation and/or processing of ingestion-related interoceptive cues (reviewed in Sections 2 and 4). However, the possibility that hippocampal neural activity is critical during the early postprandial period because that is when critical food-related postingestive cues are available is not supported by the finding that dHC inactivation given after the completion of a saccharin meal promotes the initiation of the next saccharin meal and increases the amount consumed during that meal (Hannapel et al., 2019), and that the effects of inactivation given after the end of a saccharin meal are time-dependent (Briggs et al., 2021). In these experiments, animals are given limited exposure to saccharin to reduce the likelihood of any conditioned responses to the taste. Under such conditions, saccharin has minimal postingestive consequences (Foletto et al., 2016; Mook et al., 1980; Renwick, 1985, 1986; Sclafani & Nissenbaum, 1985) and unlike sucrose, saccharin meal size and meal frequency are controlled primarily by oropharyngeal satiety (Kushner & Mook, 1984; Mook et al., 1980; Mook et al., 1981; Renwick, 1985, 1986; Sclafani & Nissenbaum, 1985). Nonetheless, the possibility remains that dHC inhibition disrupts saccharin intake by

interfering with the processing of any mechanical stimulation produced by the saccharin solution in the gut (Waise et al., 2018).

3.2. Ingestion increases biomarkers of synaptic plasticity in dHC

Collectively, the findings reviewed in the previous section demonstrate that dHC glutamatergic neural activity during the early postprandial period, when the memory of a meal is likely undergoing consolidation, is critical for dHC inhibition of future intake. If dHC neurons limit intake through a process that requires meal-related memory, then ingestion should increase events necessary for synaptic plasticity in dHC glutamatergic neurons during the early postprandial period because plasticity in these synapses is critical for memory formation (Ashby et al., 2021; Bartsch & Wulff, 2015). The most common forms of synaptic plasticity depend on glutamate NMDA receptor (NMDAR)-dependent increases in intracellular calcium that activate proteins and stimulate mRNA synthesis and protein translation that act collectively to increase glutamatergic AMPA receptor (AMPAR) function in postsynaptic cells, thereby increasing glutamatergic signaling and synaptic strength (Bengtson & Bading, 2012; Clark et al., 2015; Czerniawski et al., 2012; Kent et al., 2007; Maggio et al., 2015; Portero-Tresserra et al., 2014; Xia & Storm, 2012; Zhu et al., 2014). Posttranslational modifications of AMPAR function occur early in the induction of synaptic plasticity. For instance, long-term potentiation (LTP)-inducing stimuli and learning increase phosphorylation of serine 831 ($pSer^{831}$) residues on AMPARs (Whitlock et al., 2006). Elevations in AMPAR $pSer^{831}$, in turn, increase synaptic strength by augmenting AMPAR conductance and by promoting insertion of AMPARs in postsynaptic spines (Derkach et al., 1999; Hu et al., 2007; Kristensen et al., 2011). In support of the prediction that ingestion

induces synaptic plasticity in dHC glutamatergic neurons, Parent and colleagues showed that consuming sucrose increases AMPAR pSer^{831} in dHC neurons (Ross et al., 2019), and of note, that the magnitude of the increase is comparable to that produced by learning (Whitlock et al., 2006). Also, as in the case of learning (Whitlock et al., 2006), the effect is selective such that ingestion activates pSer^{831} but not pSer^{845} (Ross et al., 2019). Learning events also stimulate the expression of activity-regulated cytoskeleton-associated protein (*Arc*) mRNA in dHC glutamatergic neurons (Descalzi et al., 2019; Guzowski, McNaughton, et al., 2001; Guzowski, Setlow, et al., 2001; Hudgins & Otto, 2019; Tripathi et al., 2020). *Arc* is considered a master regulator of synaptic plasticity that is downstream of many molecular signaling pathways, and critically, it is necessary for many types of synaptic plasticity and for memory consolidation (Bramham et al., 2008; Korb & Finkbeiner, 2011; Shepherd & Bear, 2011). As in the case of learning experiences, Parent and colleagues showed that ingestion of sucrose or saccharin solutions increase dHC Arc nuclear mRNA levels (Henderson et al., 2017; Henderson et al., 2016), which is significant because unlike other immediate early genes, *Arc* expression reflects synaptic plasticity rather than neuronal activity (Carpenter-Hyland et al., 2010; Fletcher et al., 2006; Guzowski et al., 2006). The *Arc* data support the hypothesis that consuming a meal induces glutamatergic-dependent synaptic plasticity in dHC given that *Arc* mRNA expression is NMDAR-dependent (Czerniawski et al., 2011; Link et al., 1995; Lyford et al., 1995; Steward et al., 1998) and is required for dHC-dependent synaptic plasticity and memory (Guzowski et al., 2000). Interestingly, chronic reductions in dHC NMDAR function interferes with the ability to form and remember an association

between a taste and gastric discomfort, although whether the manipulation interferes with the ability to sense or process gastric discomfort is unclear (Chinnakkaruppan et al., 2014).

Evidence suggests that familiarity and repetition decrease dHC involvement in memory (Packard & McGaugh, 1996). Similarly, familiarity also decreases the ability of learning to increase dHC hippocampal expression of several molecules critical for memory, including Arc (Gardner et al., 2016; Guzowski et al., 2006; Guzowski, Setlow, et al., 2001; Kelly & Deadwyler, 2002, 2003), phosphorylated cAMP response element-binding protein (pCREB)(Moncada & Viola, 2006) and protein kinase M-ζ (Moncada & Viola, 2008). Thus, one prediction is that the ability of ingestion to activate the molecular processes underlying synaptic plasticity and memory formation should also decrease with repeated consumption in the same context. To test this prediction, rats were given access to a sucrose solution 10 min/day for 3, 5, or 10 days in the same context . The results showed that the amount of previous sucrose experience impacted the ability of sucrose ingestion to elevate $pSer^{831}$ in dHC. Specifically, sucrose consumption increased dHC $pSer^{831}$ in rats given 3 days of sucrose exposure, but not in rats given 5 or 10 days of exposure (Ross et al., 2019). As the amount of preceding sucrose experience increases there is a trend for a linear decrease in the amount of sucrose-induced dHC $pSer^{831}$. This finding is consistent with previous findings showing that the ability of a stimulus to activate $pSer^{831}$ depends on the history of synaptic activation (Lee et al., 2000) and that increased sucrose experience also appears to attenuate sucrose-induced increases in dHC *Arc* expression (Henderson et al., 2016). Together, the *Arc* and $pSer^{831}$ results suggest that repeated consumption of the same meal may decrease the mnemonic demands associated with that meal, the amount of neural activity required to

remember that meal and/or diminish the role of the dHC in remembering the last meal when the energy source is not novel and consumed habitually in the same context.

3.3. Future directions

Studies are needed to determine whether postmeal manipulations that increase subsequent intake do indeed impair memory of the preceding meal. The comparable effects of training and ingestion on dHC expression of biomarkers of synaptic plasticity and memory suggest that increased dHC pSer^{831} and *Arc* expression are molecular events underlying the memory of a meal. Additional experiments are needed, however, to determine whether these events are necessary for dHC control of future intake. The findings with saccharin may help identify the variables that influence the ability of ingestion to induced synaptic plasticity and by extrapolation, the memory of a meal. Specifically, the finding that saccharin ingestion induces *Arc* expression in dHC neurons (Henderson et al., 2016) and that inhibition of these neurons during the early postprandial period increases future saccharin intake (Briggs et al., 2021; Hannapel et al., 2019) suggest that the act of ingestion, orosensation, and/or mechanical stimulation of the gut are sufficient to engage meal-related synaptic plasticity and that calories are not necessary. Future experiments are needed to further identify what is being remembered in a meal, whether manipulations that augment dHC function *decrease* subsequent intake and the neural circuitry through which dHC neurons control ingestive behavior. To date, evidence suggests that dHC glutamatergic neurons limit intake via effects on neurons in the septal area (Azevedo et al., 2019), but whether these neurons are the same ones that are critical during the postprandial period remains to be determined. Another critical question is how cues

associated with energy status interact with neural mechanisms involved in memory to control eating, which is the subject of the next section.

3.4 Interim Summary

- dHC glutamatergic neurons appear to mediate the ability of meal-related memory to inhibit later intake observed in humans.
- Ingestion activates molecular processes critical for plasticity and memory in dHC during the early postprandial period.
- Neural activity during the early postprandial period is critical for dHC glutamatergic neurons to inhibit future intake.
- dHC neurons limit homeostatic (i.e., intake of standard chow), hedonic (i.e., sucrose) and non-caloric (i.e., saccharin) feeding.

4. ENDOCRINE AND NEUROPEPTIDE SYSTEMS ACT IN THE VENTRAL HIPPOCAMPUS TO REGULATE LEARNED ASPECTS OF EATING BEHAVIOR

The hippocampus is critical for the processing of interoceptive cues that inform about energy status (e.g., “hunger” and “satiety” cues). This notion is supported by data discussed above (see Section 2.1) in which bilateral damage to the hippocampus in humans is associated with disrupted awareness of hunger and satiety status. A similar phenomenon is observed in rodents with selective lesions to the hippocampus, based on experiments utilizing the deprivation intensity discrimination procedure. In this procedure, rats are trained to discriminate between a high (e.g., 24 hours) and a low (e.g., 1 hour) level of food restriction as interoceptive predictive stimuli for either positive reinforcement or positive punishment (sucrose pellets or foot shock, respectively). While intact rats are capable of

learning the deprivation intensity discrimination task, rats with selective hippocampal lesions are impaired in either acquisition of this type of learning (Davidson & Jarrard, 1993; Hock & Bunsey, 1998) or in retention of the discrimination when lesions occur after the acquisition phase (Davidson et al., 2010). Moreover, similar to patients with amnesia who accept and consume multiple consecutive meals, selective hippocampal lesions in rats leads to increased spontaneous meal frequency (Clifton et al., 1998), an outcome likely contributing to an overall increase in caloric intake and body weight gain (Davidson et al., 2009). Thus, findings from both humans and experimental rodent models indicate that the hippocampus is functionally linked with the processing of interoceptive cues that provide information about energy status.

An important yet unanswered question is whether the hippocampus is required for the sensory detection of interoceptive energy status signals vs. the interpretation of these cues via integration with mnemonic processes. The latter is more probable, as hindbrain processing alone is sufficient for basic satiation responses (based in part on data from the decerebrate rat model) (Grill & Hayes, 2012), and the hypothalamus has long been regarded as a key region for nutrient sensing and energy balance control (Timper & Bruning, 2017). Further, that the hippocampus interprets interoceptive cues based on previous learned experiences is consistent with various models of hippocampal function, including Richard Morris's model that the hippocampus resolves the "predictable ambiguity" of stimuli (Morris, 2007). Regardless of whether or not the hippocampus is required for the sensory detection of energy status cues, which again is unlikely, it is nevertheless clear that the hippocampus serves a critical role in processing cues that fluctuate based on energy status

to appropriately guide behavioral outcomes, including food seeking and eating. The locus of these interoceptive hunger and satiety signals and the precise signaling mechanisms through which they communicate with hippocampal neurons are incompletely understood.

Here, we argue that interoceptive energy status-relevant cues are communicated to the hippocampus, at least in part, via endocrine and neuropeptide systems that fluctuate either directly or indirectly with changes in energetic status. Hippocampal neurons indeed express receptors for a number of such signals, including three systems that we discuss in more depth below: ghrelin, leptin, and glucagon-like peptide-1 (GLP-1). Evidence is reviewed that these peptide systems communicate with hippocampal neurons, predominantly in the rodent vHC, to either directly or indirectly impact food-motivated behavior and/or eating behavior. Building off models proposed by Davidson, Kanoski, and colleagues (Davidson et al., 2019; Davidson et al., 2005; Kanoski & Grill, 2017), the collective data support a framework through which these endocrine and neuropeptide signals resolve the ambiguity of food-associated cues to influence various aspects of eating, including both appetitive responses and meal size control. While there are various energy balance-relevant peptide systems with receptor expression in the hippocampus that have been shown to be relevant for plasticity and memory function, such as insulin (Ferrario & Reagan, 2018), the subsequent subsections highlight systems where direct relevance to eating and/or food-motivated behaviors have been extensively investigated.

4.1. Ghrelin

Ghrelin is a stomach-derived 28-amino acid hormone that increases appetite and food intake via action on its seven transmembrane G-protein-coupled receptor, the type 1a

growth hormone secretagogue receptor (GHSR1a) (Howard et al., 1996; Sun et al., 2004). Ghrelin levels are elevated during energy restriction and prior to anticipated eating (Blum et al., 2009; Davis et al., 2011; Drazen et al., 2006; Wren et al., 2001) and decrease following a meal (Ariyasu et al., 2001; Cummings et al., 2001; Nass et al., 2008). Importantly, the rise in ghrelin levels prior to anticipated eating exceeds that induced by energy restriction alone (Drazen et al., 2006), suggesting that its release is potently influenced by learned and other cognitive factors. Ghrelin's impact on eating behavior is multifaceted, such that it influences both learned aspects of eating (e.g., conditioned appetitive responses; reviewed in (Hsu et al., 2016) as well as meal size control by interacting with vagally-mediated within-meal satiation signaling (Cabral et al., 2017; Cao et al., 2016; Levin et al., 2006; Suarez et al., 2020). GHSR1a is expressed in hippocampal neurons with particularly dense expression observed in vHC (Mani et al., 2014). Direct application of ghrelin to the vHC in rats approximately doubles food intake levels a few hours after injections by increasing both meal frequency and size, whereas ghrelin delivered to the dHC has no effect (Kanoski et al., 2013).

A role for vHC ghrelin signaling in learned aspects of eating behavior is directly supported by two key results. First, vHC ghrelin administration increases meal frequency in rats in response to auditory cues that were previously associated with palatable food access, but not in response to auditory cues not associated with food access (Kanoski et al., 2013). Second, while GHSR blockade in the vHC has no effect on consumption of either chow or a high-fat diet under free-feeding conditions, vHC GHSR blockade significantly reduces chow intake in meal-entrained rats when the antagonist is delivered immediately

before an anticipated meal (Hsu et al., 2015). Both results are consistent with a framework in which vHC ghrelin signaling resolves the ambiguity of food-associated cues to stimulate eating; the former result exemplifying a response to external discrete cues, the latter a response based on temporal circadian cues. A more recent report builds on this work by revealing that vHC GHSR signaling increases meal size by diminishing the efficacy of various within-meal satiation signals via a descending hypothalamic (orexin neurons in the lateral hypothalamic area) to hindbrain (laterodorsal tegmental nucleus) pathway. This report also revealed that vHC ghrelin injections produce an interoceptive state that generalizes to 24-hour food restriction (in otherwise nonrestricted rats) in the deprivation intensity discrimination procedure described above (Suarez et al., 2020). This latter outcome is important, as it suggests that the extent to which a high level of food restriction can disambiguate food cues by increasing their capacity to drive an appetitive response may be based, in part, on GHSR1a action in the vHC. Collectively, these results are consistent with a model in which vHC ghrelin signaling stimulates both meal frequency and meal size by resolving the ambiguity of both external and internal food-associated cues; that is, by increasing the potency of various cues to contribute to either the initiation or continuation of eating.

4.2. Leptin

Leptin is a hormone produced principally from white adipocytes (Zhang et al., 1994). Leptin receptor (LepRb) signaling potently reduces food intake and body weight; whereas, downregulation of leptin signaling through mutation of leptin or LepRb results in hyperphagia and extreme obesity in both humans and rodents (Leshan et al., 2006). While

the effects of CNS LepRb signaling on energy balance have largely focused on the hypothalamic arcuate nucleus (Myers et al., 2009); the caudal brainstem (Grill & Hayes, 2012; Hayes et al., 2010; Kanoski et al., 2012), and ventral tegmental area mesoaccumbens dopamine signaling (Fulton et al., 2006; Hommel et al., 2006), LepRb is also robustly expressed in the hippocampus (Scott et al., 2009). In opposition to ghrelin effects discussed above, activation of either dHC or vHC LepRbs produces modest but significant reductions in food intake 24 hours after injections, with more potent effects observed following vHC than dHC delivery (Kanoski et al., 2011).

In addition to reducing consumption of chow during free-feeding conditions, vHC leptin signaling also reduces conditioned appetitive behaviors. For example, vHC leptin administration reduces food seeking in an environment that has been associated with consuming a palatable meal (expression of conditioned place preference [CPP]). Further, vHC LepRb activation reduces the latency to obtain palatable food in an operant runway procedure and blocks memory consolidation for the spatial location of food (Kanoski et al., 2011). One interpretation of these results that is consistent with the framework introduced above is that hippocampal leptin signaling modulates memory formation and retrieval in a manner that actively reduces the saliency of food-related features in the environment in favor of nonfood features, resulting in reduced appetitive responding in the presence of environmental food-associated cues. In this regard, when leptin levels are endogenously high (during energy balance or surplus), this system may be signaling to the vHC (and likely other regions) to resolve the ambiguity of food cues by suppressing the memory of the

reinforcement associated with these cues (eating), which in turn reduces food-motivated behavior in response to these cues.

4.3. GLP-1

GLP-1 is a hormone produced in the distal small intestines that also functions as a neuropeptide produced in the caudal brainstem. Circulating peripheral levels of GLP-1 increase during eating (Holst, 2007) and the caudal brainstem GLP-1 neurons are engaged by various factors, including stomach distension (Vrang et al., 2003), consuming food to satiation (Kreisler & Rinaman, 2016), and following either interoceptive or psychogenic stress (Holt et al., 2019; Rinaman, 1999). While both the peripheral and central GLP-1 systems are associated with reductions in energy intake, recent evidence indicates that these two populations of GLP-1-producing cells influence eating via independent mechanisms (Brierley et al., 2021). GLP-1Rs are expressed throughout the neuraxis and activation of central GLP-1Rs reduces food intake when agonists are applied to any one of various CNS regions, including (but not limited to) the hypothalamus (Lopez-Ferreras et al., 2018; McMahon & Wellman, 1998; Schick et al., 2003), caudal brainstem (Fortin et al., 2020; Hayes et al., 2011; Hayes et al., 2008; Kinzig et al., 2002), and mesolimbic dopaminergic circuitry (Alhadeff et al., 2012; Dickson et al., 2012; Dossat et al., 2011). GLP-1Rs are also expressed in hippocampal neurons, particularly in the vHC subregion (Merchenthaler et al., 1999). Given that GLP-1 neurons do not project to the hippocampus, the source of GLP-1 signaling to hippocampal neurons is unknown, either coming from periphery to brain signaling (blood-brain barrier transport), or from volume transmission signaling from GLP-1-producing brainstem neurons, likely via humoral-like release into the

cerebrospinal fluid (Hsu et al., 2015; Noble et al., 2018). Regardless of the endogenous signaling pathway, activation of vHC GLP-1Rs potently reduces food intake in rats, with ~40-50% reduction in caloric intake 24 hours after injections based on reduced meal size with no effect on meal frequency (Hsu et al., 2015). These intake-reducing effects are physiologically relevant to normal eating, as blockade of vHC GLP-1Rs increases food intake under free-feeding conditions.

GLP-1 signaling also reduces the expression of learned food-motivated appetitive responses. First, vHC GLP-1R agonism reduces motivated lever-press responding for palatable food in a progressive ratio (PR) reinforcement schedule in which each subsequent reinforcer earned requires a higher number of lever presses than the previous reinforcer (Hsu et al., 2015). Second, vHC GLP-1R agonism (via downstream medial prefrontal cortex signaling) reduces impulsive operant responses for palatable food in the differential reinforcement of low rates of responding test (DRL), in which animals must refrain from pressing a lever for a subsequent reinforcer for at least 20 seconds to maximize the number of pellets earned in a session (Hsu et al., 2018). The rats were trained in DRL under *ad libitum* fed conditions, but were tested following 24-hour food restriction. Interestingly, increased vHC GLP-1R activation produced levels of impulsivity that mirrored levels observed at the end of training under food-sated conditions. This suggests that, in contrast to vHC ghrelin signaling replicating the effects of 24-hour food restriction in the deprivation intensity discrimination procedure, vHC GLP-1 signaling is replicating the effects of satiety on impulsive responding for food in the DRL task.

While vHC GLP-1 signaling reduced appetitive responses for palatable food in both the PR and DRL procedures, unlike vHC LepRb signaling, activation of GLP-1R in the vHC has no effect on CPP expression for a location previously associated with palatable food access. It is interesting to note that these former two tests (PR and DRL) involve testing under conditions that allow for periodic food consumption (albeit below levels to induce satiation). The CPP test, on the other hand, occurs under conditions without food access or consumption. Given that GLP-1 release, at least from the periphery, is prandial in nature (occurs during eating), it is tempting to speculate that vHC GLP-1 signaling, similar to vHC leptin signaling, reduces the effectiveness of conditioned food cues to promote appetitive responses, but unlike with leptin signaling, this capacity requires some nutrient consumption to actually occur. Within the framework of the model discussed within this section, the capacity of vHC GLP-1 signaling to reduce the ambiguity of food-associated cues (towards reducing their efficacy to promote further appetitive responses or eating) may interact with other signaling systems whose levels fluctuate during eating. One candidate system is insulin, as insulin receptors are robustly expressed in hippocampal neurons (Grillo et al., 2019), and GLP-1 signaling in the periphery promotes glucose-dependent insulin release from the pancreas (Holst, 2007).

4.4. Concluding framework and future directions

Data discussed above from rodent models identify a prominent role for vHC processing of energy balance-relevant endocrine and neuropeptide systems to influence both food-motivated responses as well as caloric consumption. Results were reviewed from experiments targeting either orexigenic (ghrelin) or anorexigenic (leptin, GLP-1) systems.

Given the evidence reviewed herein and the findings that both humans and rodents with hippocampal damage are impaired in interpreting and utilizing hunger and satiety cues to appropriately guide behavior, we propose that the hippocampus, particularly the vHC subregion, processes energy balance-relevant cues, in part, through endocrine and neuropeptide ligand-receptor binding mechanisms. In some cases, activation of these systems appears to replicate the effects of energy restriction (vHC ghrelin signaling in the deprivation intensity discrimination task) or satiety (vHC GLP-1 signaling in the DRL impulsivity test) on learned food-motivated responses. We posit that these hippocampal signaling pathways, much like hunger and satiety, function to disambiguate food-associated cues to bias behavior towards (ghrelin) or away from (leptin, GLP-1) food-directed behavior and/or continued consumption.

We conclude this section by highlighting two underdeveloped areas for future investigation: [1] The examination of potential interactions between different peptide systems acting in hippocampal neurons to modulate food-directed responses. In addition to the possible GLP-1 and insulin hippocampus signaling interaction alluded to above, recent results show that vHC ghrelin injections at doses subthreshold for intake effects alone attenuate the food intake-reducing effects of peripheral GLP-1 analog administration (Suarez et al., 2020), suggesting possible opposing interactions between these systems. [2] Investigation into the role of feeding-relevant hypothalamic neuropeptide systems on hippocampal-mediated processing of energy status information. Indeed, the hypothalamic neuropeptide melanin-concentrating hormone (MCH) is influenced by energy status and acts in the vHC to increase impulsive responding for palatable food (without affecting

consumption under free-feeding conditions) (Noble et al., 2019). Hippocampal neurons also express receptors for the hypothalamic neuropeptides, orexin (orexigenic) and oxytocin (anorexigenic), whose role in the hippocampus has been explored with regards to memory (Mavanji et al., 2017) and social behaviors (Lin et al., 2018), respectively, but not for potential roles in eating-relevant behaviors.

4.5. Interim Summary

- Hippocampal lesions in rodents disrupts discrimination learning based on varying hunger and satiety states, suggesting that the hippocampus is functionally linked with the processing of interoceptive energy status cues.
- Emerging evidence indicates that energy status-relevant cues are communicated to the hippocampus via endocrine and neuropeptide systems that fluctuate with changes in energetic status.
- The vHC is particularly sensitive to energy status-relevant peptide signals.
- Both orexigenic (ghrelin) and anorexigenic (leptin, glucagon-like peptide 1) peptide systems act in the vHC to modulate both eating and conditioned food-motivated behaviors.

5. OBESITY IS ASSOCIATED WITH IMPAIRED MEMORY AND DEFICITS IN MEMORY-RELATED NEURAL ACTIVITY IN HUMANS

Obesity is an epidemic in the Western world and is linked to overconsumption of energy dense food (Ng et al., 2014; Stevens et al., 2012). The role of learning and memory in

the regulation of consumption is of significant import when placed in the context of mounting evidence that obesity is associated with impairments in cognition (Farruggia & Small, 2019; Smith et al., 2011). Of particular relevance is a consistent finding of reduced memory ability in individuals who are obese (Cheke et al., 2017; Cheke et al., 2016; Coppin et al., 2014; Dye et al., 2017; Loprinzi & Frith, 2018; Nguyen et al., 2014; Prickett et al., 2015; Spitznagel et al., 2015). Overweight and obesity are linked with memory deficits across the lifespan, with evidence for the association in children and adolescents (Bozkurt et al., 2017; Maayan et al., 2011), young, otherwise healthy adults (Cheke et al., 2016), and older age (Benito-León et al., 2013; Beydoun et al., 2008). In a relatively small (N=50) study of nondiabetic 18-35 year olds, Cheke and colleagues (2016) investigated whether performance on item, spatial, temporal or associative "what-where-when" memory varied as a function of BMI. They found a significant negative association between BMI and performance on all tasks, with no interaction between BMI and number of items to be remembered (memory difficulty) or reaction time. Individuals with higher BMI made a comparable number of errors in terms of "total forgetting" or "spatial imprecision" but differed significantly from those with lower BMI in terms of "binding" errors, in which correct elements were incorrectly combined into item-location-time conjunctions. These findings suggest that BMI was predictive of lower memory ability specifically, rather than of general deficits (which might be expected to produced increasing deficits as difficulty increases) or reduced motivation or attention (which might be expected to alter reaction times). One advantage of this study is that it provides some predictions about whether we might expect obesity to be associated with impaired performance in all aspects of episodic

memory, (and therefore, likely consistent findings across different types of memory tasks (Cheke & Clayton, 2013, 2015) or whether the deficits may be more specific to particular memory demands. Based on Cheke and colleagues' findings, it might be predicted that all memory tests (emphasizing item, spatial or temporal information) would be impaired, but that there may be a particular deficit in associative memory. However, this study has been criticized because the effect of BMI on associative memory dropped below significance once multiple demographic factors (age, sex, education) were controlled for, although this is hard to interpret given the limited power to control for multiple factors.

A further criticism of studies such as Cheke and colleagues (2016) pertains to the reliance on body mass index (BMI) as its measure of obesity. BMI is a standard metric, useful both because it is calculated from easy to obtain measures (height and weight) and because it has well defined cut-offs: Somebody is "obese" if they have a BMI above 30. However, BMI has a number of issues (Price et al., 2006; Stevens et al., 2008). In particular, this measure makes an equivalence between bodyweight and body*fat*, which can lead to multiple confounds (e.g., from muscle mass and pregnancy). Studies using only BMI also do not allow for exploration of *which* obesity-related factor is linked with memory deficits. Multiple conditions that are highly comorbid with obesity have the potential to impact cognitive function. In a review of multiple studies, (Farruggia & Small, 2019) conclude that the evidence supports both adiposity and insulin resistance, which is highly comorbid with obesity (Khaodhiar et al., 1999), having independent (but potentially interacting) influences.

A small number of studies have attempted to disentangle the relative influence of different obesity-related factors on memory and cognition. Hartanto and Yong (2018)

investigated whether obesity as measured by BMI was a predictor of episodic memory performance when multiple factors were taken into account, and how this relationship compared against another measure of obesity- waist-hip ratio (WHR). In a sample of 4,206 participants from the MIDUS II cohort (Ryff & Lachman, 2010), they assessed BMI and WHR alongside a number of other variables relating to demographics, health and personality. They found that BMI was significantly negatively related to episodic memory (word list) performance when accounting for demographics, but not when health variables (including hypertension, diabetes and stroke) were included in the model. In contrast, WHR was negatively associated with memory performance regardless of which factors were included, suggesting that this measure is a more reliable predictor. Given that WHR is a more direct measure of visceral fat than overall BMI, this may speak to the relative influence of different types of bodyfat on cognitive function. A greater influence of visceral as compared to general or peripheral obesity on cognition is mechanistically credible, given that visceral fat is thought to be a major site of inflammatory cytokine production (Gil et al., 2011; Samaras et al., 2010). The role of inflammation in linking obesity and memory deficits is further supported by the findings of (Cook et al., 2017) who investigated the association between obesity and cognition in nondiabetic young women. They found that participants with obesity scored lower on a range of cognitive tasks including memory and that this result did not change when adjusted for depressive symptoms and physical activity. However, adjustment for inflammatory markers rendered the association nonsignificant, suggesting that this measure may mediate the impact of obesity.

Direct and indirect measures of adiposity have also been linked with both structural and functional changes in the brain, and particularly in areas linked with memory (Willette & Kapogiannis, 2015). Obesity is associated with reduced global brain volume (Beyer et al., 2019), incorporating both white matter and grey matter changes (Geha et al., 2017; Metzler-Baddeley et al., 2013), which seem to be modulated by age (Caunca et al., 2019). A recent study by Lynch and colleagues (2021) in children and adolescents found that age-corrected BMI was negatively associated with spatial memory and that this effect was partially mediated by reduced radial thickness in the left anterior hippocampus. This reflects a wider literature indicating that obesity and metabolic syndrome are associated with reductions in grey matter volume (GMV) in memory-relevant regions in childhood (Bauer et al., 2015; Chaddock et al., 2010; Mestre et al., 2017; Nouwen et al., 2017; Yau et al., 2014), although the picture may be less clear in adolescence (Lynch et al., 2021). This association continues throughout the lifespan into midlife (Debette et al., 2010) and older age (Metzler-Baddeley et al., 2013). Once again, the precise contribution of obesity, rather than comorbid conditions, is unclear. For example, patients with type 2 diabetes show reduced GMV in medial temporal and frontal regions (Moran et al., 2013), and plasma glucose and years of diabetes are positively associated with degree of brain atrophy (Tiehuis et al., 2008). The greater predictive value of WHR is supported by neural evidence from a recent study using samples from the UK Biobank (Hamer & Batty, 2019). However, here it was found that it was those who had *both* high BMI and high WHR who showed the most significantly reduced levels of GMV, compared to those who were high in only one or the other. While alterations to grey matter are pertinent to cognitive function, white matter

changes may be particularly salient with regard to the role of memory in regulating consumption. For example, the fornix links the hippocampus with the hypothalamus and hypothalamic area (Kim et al., 2012; Poletti & Creswell, 1977) as well as areas involved in the hedonic control of consumption, such as the nucleus accumbens and orbitofrontal cortex (Blatt & Rosene, 1998). Fornix microstructure is associated with memory ability and is altered in older adults with higher BMI (Metzler-Baddeley et al., 2013; Stanek et al., 2011).

The obesity-related changes in brain structure are also reflected in function. Cheke and colleagues (2017) showed that higher BMI in young healthy adults was associated with reduced activity throughout the core memory network during tasks assessing episodic memory. In particular, in the hippocampus and angular gyrus, which are areas implicated in memory integration and precision (Richter et al., 2016; Yazar et al., 2014). The authors also found that there was a similar, yet distinct, pattern of group differences in brain activity if the participants were grouped by fasting plasma insulin rather than BMI, suggesting that both adiposity and insulin resistance might be contributing to neural changes, but that one did not directly explain the other.

5.1. Diet and cognition in humans

According to the vicious cycle hypothesis, excess intake disrupts the functioning of brain areas critical for memory, which further increases intake and contributes to the development and/or maintenance of diet-induced obesity (Clasen et al., 2020). However, while it is clear from the review above that obesity is indeed associated with memory impairments, it is not apparent whether poor diet must necessarily be associated with

memory deficits *via* body fat accumulation and obesity (including associated comorbidities), or whether it is the diet itself that is detrimental. There is a substantial body of evidence linking quality of diet to cognition and brain health. However, the precise associations can be difficult to untangle in studies on humans: Experiments are rarely able to control participant diet, and thus directly measuring dietary nutrients often involves either blood sampling or supplementation, which can be difficult and expensive. Instead, most studies of the impact of diet on cognition make use of "food frequency questionnaires" (FFQs), which assess via self-report the relative abundance of particular indicator foods in a person's diet during a particular period of time. However, the reliability of these questionnaires has been challenged (e.g. Archer et al., 2018) and it is pertinent to note that measures of dietary intake that rely on *memory* for what has been consumed may lead to issues of circularity when considering the impact of diet on memory, and particularly on memory for what has been consumed. Studies of "whole diets" or the frequency of particular foods (e.g., sugar-sweetened beverages or "junk food") in the diet have identified a number of consistent patterns (Kim & Kang, 2017; Muñoz-García et al., 2020; Wiles et al., 2009). For example, "processed food" diets have been associated with poorer memory and increased risk of cognitive deficit (Akbaraly et al., 2009). Other studies have explored the importance of individual nutrients from levels estimated from FFQs. In particular, much focus has been placed upon the levels of dietary "bad" (saturated/trans) fats and "bad" (refined) sugars (Yeomans, 2017). These two nutrient groups are often studied together as a "high energy" or "Western Diet" (eg. Kanoski & Davidson, 2011). Doing so avoids many of the issues involved in trying to isolate the precise contribution of each nutrient (e.g., sugars or fats) to

deficits, acknowledging that each may contribute and that it is potentially the combined impact of a diet high in *both* saturated fat and refined sugar that that is specifically deleterious (see for example, research suggesting ketogenic diets may be neuroprotective (e.g. Hallböök et al., 2012). Much of the evidence on the impact of diet on memory and cognition has been in the context of neurodegeneration (Eskelinen et al., 2008; Gustaw-Rothenberg, 2009; Morris, 2004; Okereke et al., 2012; Pugazhenthi et al., 2017) and age-related memory loss (Jacka et al., 2015). However, a growing number of studies of young, healthy adults have also demonstrated negative correlations between self-reported fat and sugar intake and performance on memory tests (Attuquayefio et al., 2016; Francis & Stevenson, 2011; Gibson et al., 2013).

The possible mechanisms by which an unhealthy diet may lead to deficits in memory overlap considerably with those posited for adiposity, with two of the leading candidates once again being insulin resistance and inflammation. Kheirouri and Alizadeh (Kheirouri & Alizadeh, 2019) conducted a systematic review into studies exploring the "inflammatory potential" of an individual's diet and learning and memory outcomes, mostly using the 'Dietary Inflammation Index' (Shivappa et al., 2014): A higher DII score indicates a more pro-inflammatory diet, often higher in saturated fat and refined sugar. However, see (Lawrence, 2021) for an alternative view on pro-inflammatory fatty acids. The authors found that six of seven studies that assessed dementia risk reported that a higher DII was associated with increased likelihood of symptoms (Assmann et al., 2018; Frith et al., 2018; Gu et al., 2011; Hayden et al., 2017; Kesse-Guyot et al., 2017; Ozawa et al., 2017; Shin et al., 2018). Furthermore, three of these studies specifically showed negative associations between DII

and measures of episodic memory (Assmann et al., 2018; Frith et al., 2018; Kesse-Guyot et al., 2017). While these findings point to an impact of inflammation on memory, it is not clear to what extend this is a direct result of the diet: The authors note that there were a number of other factors that differentiated individuals with high DII, including BMI.

One critique of cross-sectional, and even longitudinal studies of diet and cognition, is that they are correlational: unlike the rodent literature, it is difficult to determine whether dietary composition is a causal factor in memory deficits, or a result. There are a small number of studies that address this question. Two studies, both conducted in 2011, showed a negative influence of a short (5-7 day) exposure to experimental high fat diet on attention (Edwards et al., 2011; Holloway et al., 2011), but did not assess hippocampal-dependent memory. More recently, Attuquayefio and colleagues (2017) found a significant reduction in scores on the Hopkins Verbal Learning Task (HVLTR) in healthy adults who consumed a breakfast high in saturated fat and refined sugar for 4 days, compared with controls who consumed a low fat, low sugar breakfast matched for palatability. Finally, a study using twin-pairs from the NUtriGenomic Analysis in Twins Study found that 6-week exposure to a high-fat diet impaired memory consolidation in healthy adults (Schüler et al., 2018). As with much of the rodent literature, however, dietary intervention studies struggle with the issue of direct comparison: If diets are to be matched in calories, then reductions in one type of nutrient (e.g., fat) must be balanced by an increase in another (e.g., protein). As such, it is not always easy to isolate the relative impact of decreases in one nutrient from that of increasing the other. Notably, these dietary intervention studies were conducted for short periods, and thus participants are unlikely to have gained much, if any, weight during these

interventions. Similarly, many of the studies in young adults reviewed above were able to dissociate the effects of diet from the potential confound of adiposity by using only normal weight volunteers (e.g. Attuquayefio et al., 2016; Francis & Stevenson, 2011). These findings thus suggest that unhealthy "Western" diets may be sufficient to produce memory deficits even in the absence of obesity. However, limiting the sample in this way ignores the potential for an interrelated or cumulative effect of multiple factors.

5.2. Memory for food

The evidence therefore suggests that there may be general issues with memory in obesity, and that multiple elements of the "obese syndrome", including diet, may make independent contributions to this. These findings are significant given the importance of memory in regulating consumption. However, is there any reason to believe this may specifically impact memory for food? FMRI investigations indicate that individuals with obesity have unusual hippocampal responses to food cues, and that this is modulated by nutritive state (DelParigi et al., 2004; Geha et al., 2017; Leidy et al., 2011). In a recent study, Jones and colleagues (Jones et al., 2021) showed that lean, but not obese, participants showed greater hippocampal food-cue reactivity immediately following glucose consumption relative to water. The BMI group difference was driven by a significantly reduced level of hippocampal reactivity in individuals who were obese in the glucose condition. Reduced hippocampal response to food cues while in a post-consumptive state may suggest reduced contextualized processing of these stimuli. This would be significant both in terms of the suggested role of the hippocampus in integrating food stimuli with

contextual information about current need state (e.g. Davidson et al., 2009), but also with the likelihood that these stimuli will be retained in memory.

Evidence for memory deficits have been shown both in studies using food stimuli (Cheke et al., 2017; Cheke et al., 2016) and nonfood stimuli (Cook et al., 2017), but few studies have explicitly compared the two. Leng and colleagues tested young women with either healthy or obese BMI on a word-list source memory task including both food and non-food stimuli. They found that item memory for non-food stimuli was impaired in the group with obesity, but that recognition of food words was *better* in the group with obesity than in lean controls. Source memory was, however, impaired for both types of stimuli (Leng et al., 2021). The authors suggest that this could reflect an attentional bias towards food cues in young women who are obese, something that has been previously reported in samples with obesity (Docteur et al., 2008; Hagan et al., 2020; Soetens & Braet, 2007). According to central/peripheral trade-off theory (Kensinger, 2009), attentional biases may improve item- while impairing source-memory as the salient item "captures" disproportionate attention, reducing encoding of contextual information. Such an account may suggest that during a meal, individuals with obesity may encode the food eaten, but may be less able to integrate this information with the contextual information that renders the memory useful for regulating consumption, particularly motivational need state and time of eating.

5.3. Future directions

In summary, obesity has been associated consistently with changes in both memory and the neural structures that underpin it. There appear to be multiple, potentially mutually

exacerbating, mechanisms driving this association. Notably, a high fat, high sugar diet is sufficient to induce neural and cognitive changes itself, as well as via accumulation of bodyfat and comorbidities such as diabetes. Factors such as insulin resistance and inflammation are highly implicated by multiple lines of evidence. However, these associations are complex and can be difficult to isolate in human studies, and much can be learned from rodent models in this respect. Nonetheless, large sample longitudinal studies may be able to tease apart the relative contributions of different causal factors and should be a target of future research. In addition, the impact of short vs long term high fat diet requires further exploration: Evidence from mice suggests that 24 hours of a high fat diet may be sufficient to induce memory deficits that are then quickly reversible on return to a low fat regime (McLean et al., 2018). Is this also the case in humans, and if so, is it due to fast-acting deleterious effects, or, for example, the costs associated with the physiological transfer between primary fuel sources which may resolve with time (Cunnane et al., 2020)? The answers to these questions could have considerable implications for dietary guidance and intervention.

The combination of obesity-related changes to general and associative memory processes and alterations to food-cue reactivity may be particularly significant for understanding the factors that perpetuate obesity through dysregulated consumption. The next stage in this research will require a better understanding of how memories for consumption episodes are encoded and represented in the brain, and specifically *how* these representations are affected by obesity. It is not currently clear how the memory deficits demonstrated in obesity are manifested when it comes to remembered meals, and

subsequent changes in consumption. Such explorations are vital in closing the gaps in the "vicious cycle."

5.4 Interim Summary

- Multiple elements of the "obese syndrome" are associated with memory deficits and brain changes in humans.
- The relative contributions of adiposity and diet are difficult to isolate, and both may contribute independently.
- Obesity may be associated with particular deficits in remembering contextual details of food events.

6. IMPACT OF OBESITY ON HIPPPOCAMPAL FUNCTION IN RODENTS

The evidence reviewed above indicates that cognitive functions mediated by the hippocampus limit eating behavior and that, in humans, obesity is associated with impaired cognitive and hippocampal function. The following section will review the impact of hypercaloric foods and obesity on hippocampal function in rodents and will summarize potential mechanisms through which obesity mediates these effects. Given that hippocampal dysfunction increases energy intake, this large body of evidence provides convincing support for the possibility that diet-induced obesity is caused and/or maintained at least in part by a vicious cycle wherein overeating disrupts hippocampal function, leading to further overeating (Clasen et al., 2020).

Extensive research had shown that hypercaloric diets and the associated obesity and metabolic complications impair dHC-dependent memory, including spatial memory in the

water maze, radial arm maze, spontaneous alternation and object location tasks (Darling et al., 2013; Farr et al., 2008; Fu et al., 2017; Greenwood & Winocur, 1990; Hernández-Ramírez et al., 2021; Heyward et al., 2016; Li et al., 2002; McFadden et al., 2020; Ross et al., 2009; Ross et al., 2012; Stranahan et al., 2008; Valladolid-Acebes et al., 2012) . The memory-impairing effects of high energy diets and obesity are accompanied by deficits in dHC glutamatergic metabolism, neurotransmission (Valladolid-Acebes et al., 2012), synaptic plasticity (Farr et al., 2008; Gerges et al., 2003; Hao et al., 2016; Karimi et al., 2015; Li et al., 2002; Porter et al., 2012; Stranahan et al., 2008), and neurogenesis (Bonds et al., 2020; Bracke et al., 2019; Lindqvist et al., 2006). Obesity likely interferes with synaptic plasticity by reducing hippocampal spine density (Stranahan et al., 2008) decreasing levels of critical molecules such Arc (Mateos et al., 2009), brain-derived neurotrophic factor (BDNF) (Stranahan et al., 2008; Wu et al., 2004), and CREB (Wu et al., 2004), by dysregulating ubiquitin-proteasome signaling and protein degradation (McFadden et al., 2020), and by promoting microglia-induced synaptic stripping (Hao et al., 2016). Some of the proximal mechanisms include peripheral elevations in triglycerides based on evidence showing that lowering triglycerides reverses memory deficits and that application of triglycerides impairs synaptic plasticity (Farr et al., 2008). Given that diets low in carbohydrates and ketogenic diets effectively reduce triglyceride levels, findings showing that lowering triglyceride levels reverses memory deficits is consistent with the possibility that this may be the mechanism through which low carbohydrate and ketogenic diets exert the cognitive improvements observed in human participants described in Section 5. Elevated adiposity also increases peripheral levels of pro-inflammatory cytokines and induces neuroinflammation (Bondan et

al., 2019; Guo et al., 2020; Hao et al., 2016). Cytokines produced by adipose tissue, particularly interleukin1 (IL-1) and IL-1-mediated microglia activation in dHC have been implicated in the impact of obesity on hippocampal synaptic plasticity and memory (Erion et al., 2014; Guo et al., 2020; Hao et al., 2016). The effects of high energy diets and obesity on memory and plasticity are rescued by antioxidants, suggesting that some of their effects on the brain may also be mediated by oxidative stress (Karimi et al., 2013; Wu et al., 2004). Other contributing factors include hippocampal insulin resistance (Fu et al., 2017; Gladding et al., 2018) and epigenetic dysregulation of hippocampal genes critical for memory (Heyward et al., 2016).

In addition to impairing exteroceptive-based learning, synaptic plasticity, and other memory-associated neurobiological processes in the hippocampus, high energy diet consumption and/or obesity are also associated with impairments in hippocampal processing of interoceptive signals that inform about energy status. For example, in rats that were previously trained to discriminate between low and high levels of food restriction for appetitive reinforcement (the deprivation intensity discrimination task described in Section 4), switching from healthy chow to a high energy Western-style diet disrupted the capacity for the rats to discriminate between energetic states (Sample et al., 2016). Several findings suggest that this impaired interoceptive awareness associated with high energy diet consumption, analogous to that observed following selective hippocampal damage in rodents (Davidson et al., 2010), is based on disrupted hippocampal processing of endocrine and vagus nerve-mediated signals that fluctuate based on energy status and/or meal consumption. For example, ghrelin receptor activation in vHC neurons engages

phosphoinositide 3-kinase (PI3K) subunit p85 and AKT (Ser473) intracellular signaling pathways in chow-fed rats, but not in rats maintained on a high energy diet for 4 weeks (Kanoski et al., 2013). Given that vHC ghrelin administration replicates the effects of 24 hour food restriction in otherwise nonrestricted rats in the deprivation intensity discrimination task (Suarez et al., 2020), this suggests that high energy diet consumption reduces the capacity of ghrelin to communicate interoceptive hunger status to vHC neurons.

Consuming a high energy diet also appears to reduce the capacity of anorexigenic interoceptive signals to engage hippocampal neurons. For example, leptin administration increases dHC expression of BDNF, a neurotrophin that promotes memory formation and neural plasticity, in control rats fed a healthy chow diet but not in rats fed a high energy diet for 2 weeks (Kanoski et al., 2014). Further, the within-meal satiation signal cholecystokinin (CCK) activates dHC neurons via a vagus nerve-mediated polysynaptic pathway (Suarez et al., 2018). While this response has not been directly evaluated in obese or high energy diet-fed rodents, it has been established that high energy diet maintenance reduces the capacity of peripheral CCK to activate neurons in the hindbrain nucleus tractus solitarius (Covasa et al., 2000), the first CNS relay connecting the vagus nerve signaling to the dHC (Suarez et al., 2018). Collectively, these findings suggest that consumption of a high energy Western-style diet blunts the capacity of both hunger-associated biological signals (ghrelin) and satiation- and satiety-associated biological signals (CCK, leptin) to communicate interoceptive energy status to both the ventral and dorsal subregions of the hippocampus.

6.1 Interim summary

- Hypercaloric diets and the associated obesity and metabolic complications impair dHC-dependent memory.
- The memory-impairing effects of high energy diets and obesity are accompanied by changes in dHC glutamatergic neuronal structure and synaptic plasticity.
- Several mechanisms may collectively contribute to these alterations, including elevated triglycerides, peripheral and central inflammation, oxidative stress, hippocampal insulin resistance, and epigenetic dysregulation of hippocampal genes critical for memory.
- Hypercaloric diets and the associated obesity and metabolic complications are also associated with impaired hippocampal processing of interoceptive signals that inform about energy status.
- These deficits in interoception appear to be based on disrupted hippocampal processing of endocrine and vagus nerve-mediated hunger and satiety signals.

7. CONCLUDING REMARKS

In summary, the evidence reviewed above demonstrates that impaired memory and disrupted hippocampal functioning are associated with deficits in processing of hunger and satiety cues and overeating in both humans and rodents. Convincing evidence was presented indicating that endocrine and neuropeptide systems act primarily in vHC to provide hunger and satiety signals and regulate learned aspects of eating. Extensive findings show that meal-related memory limits future intake and this appears to be mediated, at least in part, by principal dHC neurons. The relationship between memory and eating is

bidirectional such that overconsumption of high energy diets and obesity impairs interoceptive processing, memory and hippocampal function in both humans and rodents. These disturbances, in turn, would be expected to contribute to further excessive intake, thereby creating a vicious cycle that contributes to and/or perpetuates unhealthy weight gain.

Several outstanding questions remain. For instance, although obesity is clearly associated with disruptions in many hippocampal processes, there is no equivocal evidence showing that obesity actually interferes with hippocampal-mediated inhibition of energy intake. The relationship between dHC and vHC regulation of eating is also unclear. Although there are cases when dHC and vHC involvement in eating diverges (e.g., the ability of ghrelin to stimulate intake is mediated by vHC but not dHC (Kanoski et al., 2013); there are instances when there is overlap in dHC and vHC participation in interoceptive processing and eating. For example, while endocrine signals appear to predominantly engage vHC, there is also evidence indicating that meal-related satiation signals communicating from the gut to the brain via the vagus nerve engage dHC and promote memory function (Suarez et al., 2018). Similarly, as in the case of postmeal dHC inactivation, postmeal vHC inactivation also increases consumption (Hannapel et al., 2019; Hannapel et al., 2017). Finally, neural circuits that suppress energy intake in mice have been established from both the vHC (Sweeney & Yang, 2015) and dHC (Azevedo et al., 2019) to distinct septal nuclei (lateral and medial, respectively). Given that vHC is involved primarily in emotional and food-related memory and dHC in episodic and spatial memory, both dHC and vHC may contribute to the mnemonic representation of an eating episode and inhibit subsequent intake via both

common and distinct mechanisms. Indeed, memory is mediated by multiple brain areas that each represent different information contained within the same experience (Gasbarri et al., 2014; White et al., 2013). While the focus here, and in the rodent literature more generally, is within the hippocampus, other areas within the "core memory network" may also contribute to the association between memory and eating. Future work should particularly explore those areas found to be altered in human obesity, such as the angular gyrus (Cheke et al., 2017).

Another question is whether this relationship between memory and eating can be used to identify treatments to promote weight loss. For example, it is possible that compounds that are used to treat memory problems could attenuate weight gain. The application of the results from experimental studies in humans on the role of memory for recent eating in appetite to the development of healthy eating/weight loss interventions is only beginning to be explored. A smartphone application aimed at enhancing food memories and encouraging "attentive" eating was found to be acceptable by users (Robinson, Higgs, et al., 2013), but an initial efficacy trial did not find any effects of using the application on energy intake or weight loss (Whitelock, Kersbergen, et al., 2019). An analysis of user experiences identified facilitators (e.g., ability to incorporate into routine) and barriers (e.g., older participants feeling that using the application in social settings was inappropriate) to application usage that could inform the design of future studies (Whitelock et al., 2020). Future research could also be aimed at identifying more effective ways of reliably enhancing memory for recent eating that could be used in healthy

eating/weight loss interventions and investigating whether such interventions should be targeted at individuals with lower memory ability.

Finally, evidence from weight loss interventions suggest that the negative impact of overweight on memory may be reversible (Siervo et al., 2011). Bariatric surgery studies consistently show memory deficits in pre-operative patients (Alosco, Galioto, et al., 2014; Alosco, Spitznagel, et al., 2014; Gunstad et al., 2011; Miller et al., 2013; Walø-Syversen et al., 2021). Consistent with results from preclinical rodent models (Grayson et al., 2014), many of these studies have shown that verbal memory performance is significantly improved 12 weeks following gastric bypass surgery and that these benefits are maintained at 1- (Miller et al., 2013), 2- (Alosco, Spitznagel, et al., 2014) and 3-years (Alosco, Galioto, et al., 2014) postoperative. These studies also indicated that (after controlling for initial BMI) postoperative BMI was related to memory performance, suggesting that those who returned to a healthier weight were more likely to see memory improvement. It should be noted however, that even here the causality is not clear cut: There is some evidence to suggest that cognitive performance may predict outcome following surgery, potentially via ability to maintain the strict lifestyle and medication regime required (Elfhag & Rössner, 2005; Spitznagel et al., 2015). This may suggest that those within the surgery group that had initially better cognition would be more likely to have lost more weight. Weight-loss may also be associated with neural changes: Boraxbekk and colleagues (2015) found that 6 months on a restricted diet not only improved face-name associative memory, but also that decreases in waist circumferences were correlated with increased brain activity in the superior temporal gyrus and insula. Lastly, whether effects are permanent or reversible may

depend on the key causal factor. In patients with diabetes, for example, large-scale trials of intense glycemic control have found no significant recovery of brain volume or cognition (Murray et al., 2017).

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