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The functional architecture of dehydration-anorexia

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ABSTRACT

The anorexia that accompanies the drinking of hypertonic saline (DE-anorexia) is a critical adaptive behavioral mechanism that helps protect the integrity of fluid compartments during extended periods of cellular dehydration. Feeding is rapidly reinstated once drinking water is made available again. The relative simplicity and reproducibility of these behaviors makes DE-anorexia a very useful model for investigating how the various neural networks that control ingestive behaviors first suppress and then reinstate feeding. We show that DE-anorexia develops primarily because the mechanisms that terminate ongoing meals are upregulated in such a way as to significantly reduce meal size. At the same time however, signals generated by the ensuing negative energy balance appropriately activate neural mechanisms that can increase food intake. But as the output from these two competing processes is integrated, the net result is an increasing reduction of nocturnal food intake, despite the fact that spontaneous meals are initiated with the same frequency as in control animals. Furthermore, hypothalamic NPY injections also stimulate feeding in DE-anorexic animals with the same latency as controls, but again meals are prematurely terminated. Comparing Fos expression patterns across the brain following 2-deoxyglucose administration to control and DE-anorexic animals implicates neurons in the descending part of the parvicellular paraventricular nucleus of the hypothalamus and the lateral hypothalamic areas as key components of the networks that control DE-anorexia. Finally, DE-anorexia generates multiple inhibitory processes to suppress feeding. These are differentially disengaged once drinking water is reinstated.

The paper represents an invited review by a symposium, award winner or keynote speaker at the Society for the Study of Ingestive Behavior [SSIB] Annual Meeting in Portland, July 2009.

1. Introduction

Animals have developed sophisticated neural mechanisms that allow them to organize their feeding behavior in ways that anticipate deficits in energy balance, compensate for nutrient imbalance, and adapt to large fluctuations in their food supply. As we have begun to appreciate the complexity of these mechanisms, our understanding of how the associated neural control networks are organized has increased commensurately.

Much of the basis for our current understanding of mechanism has come from observing the feeding behavior that follows central injections of neuropeptides. From this work we now know that some hypothalamic neurons contain peptides that are orexigenic (eg. neuropeptide Y [NPY], agouti-related peptide [AgRP], hypocretin/orexin), while others utilize anorexogenic peptides (eg. α-melanocyte-stimulating hormone, corticotropin-releasing hormone [CRH]). These observations suggest that at the simplest level, hypothalamic control networks are functionally organized into those that stimulate feeding and those that inhibit feeding in a manner reminiscent of the model first proposed by Stellar [1].

Although a great deal of research has now identified key components at discrete hypothalamic loci, the complex interactions between the various levels of the neuroaxis are now recognized as the key to how the brain controls motivated feeding behavior [2–6]. This view has encouraged a wider appreciation of the importance of neural networks that enable these interactions, but also the realization that a complete understanding requires that we examine how they interact functionally. The experimental model that we use to help clarify these interactions is dehydration-anorexia, which is a behavioral adaptation to the physiological challenges of cellular dehydration. Our data suggest that the suppression of feeding in these circumstances occurs because neuronal function in the paraventricular nucleus (PVH) and parts of the lateral hypothalamus (LHA) is modified in a way that suppresses feeding. This review will describe some of our recent work using cellular dehydration-induced anorexia in support to this idea.

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2. Network models for understanding the control of ingestive behaviors

The importance of the hypothalamus for all motivated behaviors is encapsulated in the model proposed by Swanson that posits the existence of a behavior control column in the medial hypothalamus [7]. Here, specific hypothalamic nuclei are associated with particular motivated behaviors. The PVH and possibly parts of the LHA are identified as being important for ingestive behaviors [7]. For this to occur, neurons in the PVH and LHA that control ingestive behaviors must rely on a variety of regulatory inputs to regulate their actions. These include exterosensory, viscerosensory, humerosensory, circadian timing information, and cognitive influences (Fig. 1), all of which are brought to the PVH and LHA by the many and varied afferents sets from the hindbrain, telencephalon, and other parts of the hypothalamus. In turn, the output of these stimulatory and inhibitory control networks that involve the PVH and LHA must at some point be integrated in a way that generates the most appropriate feeding behavior for the ongoing situation (Fig. 1).

Mechanistic details of the integrative process are currently unclear but given the complex ascending and descending outputs from PVH and LHA neurons, it seems reasonable to assume that integration occurs both inside and outside of the hypothalamus, perhaps including locations in the telencephalon, midbrain, and hindbrain. The outcome of this integration then influences the motor action selection circuits, and ultimately the pre-motor and motor neurons to appropriately enable particular behaviors (Fig. 1). Finally, once feeding behavior is initiated a variety of post-ingestive and other signals engage all levels of the motor control network to influence the structure and duration of a feeding bout.

The way that the whole network operates to stimulate feeding in both normal and pathological circumstances has been well studied for many years. However, in some situations feeding behavior is attenuated even when prevailing signals should favor increased food intake. This can lead to anorexia and body wasting (cachexia), which in humans is a serious complication for some clinical conditions.

3. Types of anorexia

The term anorexia describes any loss of appetite and concomitant reduction in food intake that occurs in the presence of readily accessible food sources. We have previously divided anorexia into two broad categories depending on whether it is an adaptive or a pathological response (Fig. 2 [6,8]).

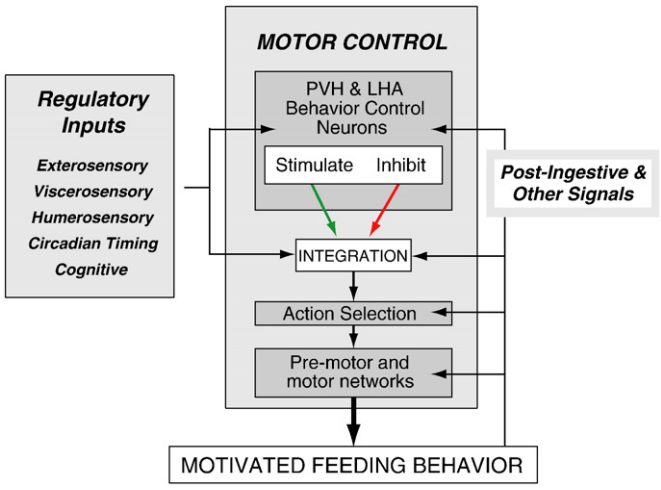

Fig. 1. A schematic representation of the functional networks that interact to control ingestive behaviors. A key feature of this model is the presence of stimulatory and inhibitory networks in the hypothalamus that are regulated by multiple inputs, including those that encode post-ingestive signals from the gastrointestinal tract. The outputs of the stimulatory and inhibitory networks are integrated to control the downstream motor control circuits.
(Adapted from [5]).

Adaptive anorexia is evident as a behavioral response to certain homeostatic challenges. Some of these may originate externally, as is the case of anorexia that accompanies some types of stress [9], or it may be an adaptive behavioral response to a physiological challenge such as the cellular dehydration that results from drinking hypertonic saline or water deprivation.

Pathological anorexia accompanies a number of disease states, and can be further subdivided into two groups. 1) Where anorexia is a primary indication. In these circumstances anorexia is widely believed to originate psychologically. In humans, anorexia nervosa is the most prominent of these conditions. 2) Where anorexia is a secondary indication that is associated with disease states. The cachexia (disease-associated wasting) that accompanies AIDS, cancer, and other conditions is perhaps the most important and widely known.

The mechanisms that generate the different types of anorexias are many and diverse, and must involve a variety of different neural networks. But from a systems perspective, it seems reasonable to assume that these different mechanisms must ultimately converge on the common set of neural circuits that are distributed throughout the brain control feeding behavior (Fig. 1).

4. Why dehydration-anorexia?

When animals are given restricted access to water or if their only fluid source is hypertonic they gradually develop hypernatremia and hyperosmolemia. The clearest outcome of this condition is increased thirst and the engagement of mechanisms that motivate drinking water. However, a critical adjunct to this response is the marked suppression of food intake: dehydration (DE)-anorexia. This response serves two purposes: first, it reduces the amount of water required for digestion thereby allowing the water to move from the gut into the rest of the body to ameliorate some of the effects of hyperosmolemia; and second, it reduces the intake of osmolytes from food. Hyperosmolemia appears to be the principal signal for DE-anorexia, and there is a strong correlation between plasma osmolality and the suppression of food intake (Fig. 3). The onset and termination of DE-anorexia are both easily controlled, and the associated behavioral sequences are highly stereotyped making alterations in behavioral structure relatively easy to correlate with changes in neuronal activity [10–12].

We will now describe how we have used DE-anorexia to clarify the organization of the networks that control feeding behavior as it is suppressed and then reactivated.

5. Network models and the functional architecture of dehydration-anorexia

Using the scheme shown in Fig. 1 we propose that there are at least four components to the mechanism used by drinking hypertonic saline to generate anorexia (Fig. 4).

First, increased activity in the stimulatory networks of the hypothalamic controller (Fig. 4 – 1); second, at the same time the activity of the inhibitory networks in the hypothalamic controller is increased in a way that blunts the influence of the stimulatory networks on feeding (Fig. 4 – 2); third, the functions of the regulatory inputs to the hypothalamic controller are unaffected by hyperosmolemia (Fig. 4 – 3); finally, neurons in the PVH and LHA that control ingestive behaviors and possibly their downstream targets are rendered less sensitive to afferent drive (Fig. 4 – 4).

The net result of the impact of drinking hypertonic saline on the hypothalamic control networks is that their integrated output now favors anorexia rather than spontaneous feeding (Fig. 4). Importantly,

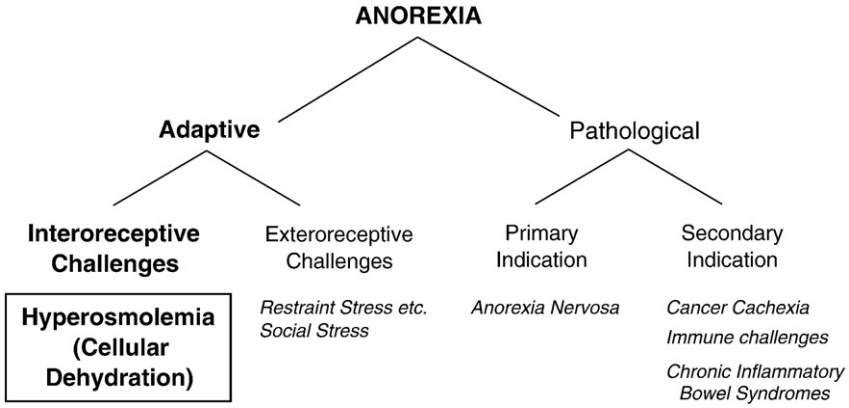

Fig. 2. Anorexia can be expressed, first, as an adaptive response that helps animals confront an imposed challenge or stressor. These responses can result from stimuli that are internally or externally generated. Dehydration anorexia is an example of an adaptive response that results from internally generated signals. Second, anorexia can develop as a response to pathological conditions, either as a primary or a secondary indication.
(Adapted from [8]).

this arrangement also allows for the rapid activation of feeding once water is returned.

5.1. The upregulation of activity in the stimulatory networks (Fig. 4 – 1)

DE-anorexic rats show all of the appropriate hormonal responses to negative energy balance: reduced plasma leptin and insulin, and elevated plasma corticosterone and ghrelin concentrations [13,14]. Plasma glucose concentrations are maintained within the normal range [15]. Furthermore, hypothalamic gene expression reflects the status of these signals: *Npy, Agrp*, and *Pomc* expression in the arcuate nucleus (ARH) are all appropriately increased or decreased [13; and D. Salter-Venzon & A.G. Watts, unpublished observations]. Neuroendocrine *Crh* expression is reduced in the medial parvicellular part of the PVH as a consequence of an interaction between hyperosmolality and increased circulating corticosterone concentrations [16,17].

Collectively these data show that DE-anorexia does not result from maladaptation of the processes that respond to negative energy balance. On the contrary, all these mechanisms appear to function quite normally, and lead to increased activity in the networks that should increase feeding.

5.2. The upregulation of inhibitory network activity (Fig. 4 – 2)

If drinking hypertonic saline suppresses feeding despite all the appropriate hormonal and neuropeptide responses to negative energy balance, then it seems reasonable to assume that there must be a similar up-regulation in the activity of networks that inhibit feeding. The net result is that inhibitory mechanisms are able to override the effects of signals of negative energy balance. Some of the inhibitory signals may derive from sensors in the gastrointestinal (GI) tract that appear to play key role in mediating DE-anorexia, at least in water-deprived rats [18].

Increased activity in inhibitory networks is perhaps most clearly evident in the structure of spontaneous meal patterns in DE-anorexic animals. We have recently employed a high-resolution meal pattern analysis, and found that although DE-anorexic animals eat the same

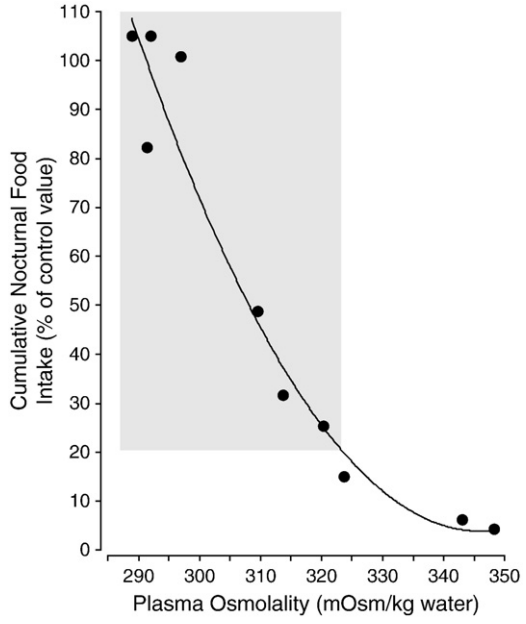

Fig. 3. The correlation between plasma osmolality and cumulative nocturnal food intake in individual rats given 2.5% hypertonic saline to drink for between 1 and 5 days. The gray rectangle shows the target range of plasma osmolalities for experiments reported in the papers discussed in this review.
(Adapted from data from [11,13]).

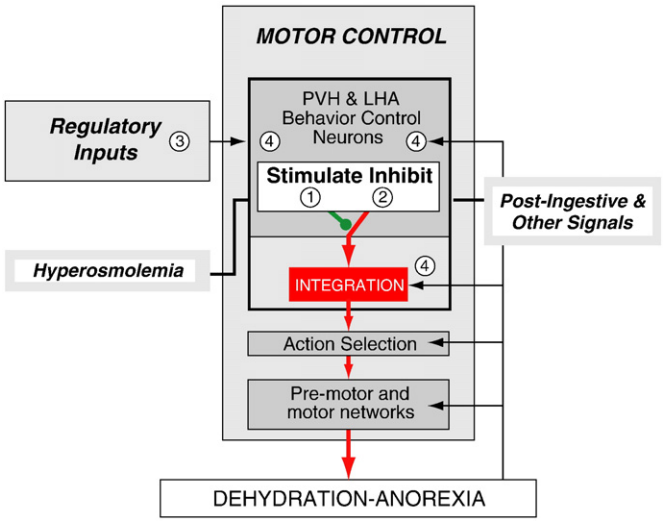

Fig. 4. A schematic representation of the functional networks that interact to generate dehydration anorexia. Stimulatory (1) and inhibitory networks (2) are both upregulated by the effects of increasing plasma osmolality and signals from the gastrointestinal tract. However, upregulated activity in inhibitory networks masks the effects from the stimulatory networks. At the same time the activity of other regulatory inputs is maintained (3), but their impact on hypothalamic neurons in the parvicellular paraventricular nucleus of the hypothalamus and the lateral hypothalamic areas, as well as their downstream targets is blunted (4). Anorexia is the net outcome of the altered processing that occurs within the key control networks in the hypothalamus and elsewhere.

number of meals as controls within a 24 h period, these are shorter in duration and smaller in size than spontaneously feeding euhydrated animals [19]. The meal patterns of DE-anorexic animals show that the mechanisms responsible for initiating feeding appears to be unaffected by drinking hypertonic saline, which is consistent with notion of normal or up-regulated stimulatory mechanisms. However, the increased activity of inhibitory networks prematurely terminates the meals.

Further evidence for this model comes from the response of DE-anorexic animals to local injections of NPY into the PVH or LHA [20]. NPY is a neuropeptide found in some ARH and hindbrain catecholaminergic neurons that project to the LHA and PVH [20,23]. NPY acts to increase feeding by directing an animal's foraging behavior towards food and by reducing the efficacy of satiety signals that terminate feeding [21,22]. Together these mechanisms increase food intake.

DE-anorexic animals injected with NPY into the PVH or LHA initiate feeding with the same latency as controls (7–9 min), but the amount of food consumed over the next hour is significantly reduced [20]. The reduced efficacy of NPY to stimulate feeding in DE-anorexic animals is site-specific; the LHA remains more sensitive to NPY than the PVH. These findings are consistent with the idea that drinking hypertonic saline does not interfere with an animal's ability to initiate feeding, but it affects control networks in such a way as to advance the termination phase of a meal and so reduce the amount eaten. Under these circumstances the ability of NPY to reduce the efficacy of satiety signals and delay meal termination is blunted.

5.3. Drinking hypertonic saline does not reduce the activity of key regulatory afferent inputs to the hypothalamic controller (Fig. 4 – 3)

One of the mechanisms that drinking hypertonic saline might use to generate anorexia is to reduce the activity of the afferent inputs that bring important metabolism-related signals to hypothalamic behavior control neurons (Fig. 1). With this model key neurons in the PVH and LHA would be unaffected by drinking hypertonic saline, but anorexia develops because their regulatory inputs would show reduced activity. We have begun to test this hypothesis by examining one set of key inputs to the hypothalamus; the catecholaminergic afferents from the hindbrain. These inputs are essential for complete glucocorticoid and feeding responses to 2-deoxyglucose (2DG) [23]. We found that if DE-anorexic animals are challenged with 2DG they generate normal and robust glucocorticoid and hyperglycemic responses, but their feeding response is significantly attenuated [15]. These results show that catecholaminergic afferents to the PVH retain their ability to stimulate glucocorticoid release in DE-anorexic animals, but the downstream effectors are compromised when it comes to stimulating feeding. Our recent Fos expression pattern results in DE-anorexic animals given 2DG also support this conclusion [24]. These results suggest that the signals from drinking hypertonic saline target those mechanisms in the PVH and LHA responsible for regulating feeding behavior rather than a wider action upon the afferents themselves. While these results only address the function of one set of afferents, they show that some key afferents to the PVH and LHA retain their ability to drive responses to metabolic challenges in DE-anorexic animals. These findings are consistent with the model where drinking hypertonic saline reduces the sensitivity of key control neurons in the PVH and LHA to afferent input.

5.4. Drinking hypertonic saline reduces the sensitivity of neurons in paraventricular nucleus and lateral hypothalamic area to afferent signals (Fig. 4 – 4)

The results that have been discussed to this point have focused on broader network structure rather than on the specific neuronal populations that are targeted in dehydrated animals to suppress feeding. To identify candidate regulatory neurons in the hypothalamus we have performed a number of studies that reveal the important role played by neurons in lateral parvicellular part of the PVH and the perifornical regions of the LHA in regulating feeding behavior during DE-anorexia.

In a broad survey of neuropeptide gene expression in the forebrain we compared patterns in control, DE-anorexic animals, and animals pair-fed to match the intake of anorexic rats. We found that the only changes exclusive to anorexic animals were increased expression of *Crh* and *Nt/Nmn* in a discrete population of LHA neurons located close to the fornix [12,13,25]. We have recently shown that in most of these LHA neurons CRH is colocalized with neurotensin [12]. Interestingly, those LHA neurons containing melanin-concentrating hormone and hypocretin/orexin are not targeted by hyperosmolemia, as determined by their Fos responses [12]. CRH/neurotensin neurons in the LHA receive direct inputs from osmosensitive neurons in the rostral hypothalamus, which are necessary for their responses to hyperosmolemia [26]. They also project strongly to the lateral parabrachial nucleus and possibly the PVH [13,27].

One of the characteristics of DE-anorexia is a reduced feeding response to 2DG [15]. We recently used a comparative pattern analysis of Fos response patterns in the hypothalamus and hindbrain of control and DE-anorexic animals given 2DG to identify candidate neurons that suppress 2DG feeding [24]. We reasoned that regions showing an altered Fos response to 2DG in DE-anorexic animals would be strong candidate targets of dehydration-induced suppression of 2DG feeding. Our results showed that the many hypothalamic and hindbrain regions that have bidirectional connections with the LHA and PVH, including the ARH, the lateral parabrachial nucleus, parts of the nucleus of the solitary tract and dorsal motor nucleus of the vagus, have unimpeded Fos responses to 2DG in DE-anorexic animals. However, Fos responses to 2DG in the lateral parvicellular part of the PVH and the perifornical regions of the LHA exhibit altered activation patterns in DE-anorexic animals compared to controls [24]. Collectively, these results show that specific neurons in the lateral parvicellular part of the PVH and perifornical regions of the LHA are specifically targeted after drinking hypertonic saline.

5.5. Feeding stimulated by drinking water: the suppression of multiple inhibitory signals (Fig. 5)

A striking feature of DE-anorexia is the rapid reinstatement of feeding once drinking water is resumed [10]. When this occurs there is an initial bout of drinking that lasts about 4–5 min, which is followed about 3–4 min later by a vigorous episode of feeding lasting about 12–15 min. Thereafter, animals alternate eating and drinking, and increase their general activity for about an hour [10,12].

As discussed earlier, the fact that DE-anorexia results primarily from a decrease in meal size while the daily number of meals remains largely unaltered suggests that up-regulated satiety is a major contributory factor (Fig. 4 – 2). At the same time however, peripheral signals of negative energy balance (decreased plasma leptin and insulin, increased plasma ghrelin) increase activity in stimulatory networks in a way that would normally stimulate feeding (Fig. 4 – 1). This arrangement suggests that one way that drinking water can stimulate feeding is simply to reduce the increased inhibition by way of falling plasma osmolality. However, this seems unlikely because feeding begins well before osmolality falls after drinking water [5,28].

A detailed comparison of meal patterns between DE-anorexic animals given back water and pair-fed animals given back food is consistent with a more complex two-step process [29]. The first part of the process is engaged immediately after water is returned and quickly disinhibits the activated stimulatory networks (perhaps in the regions where the stimulatory and inhibitory networks are integrated) to produce the initial burst of feeding (Fig. 5 – 5). One possible

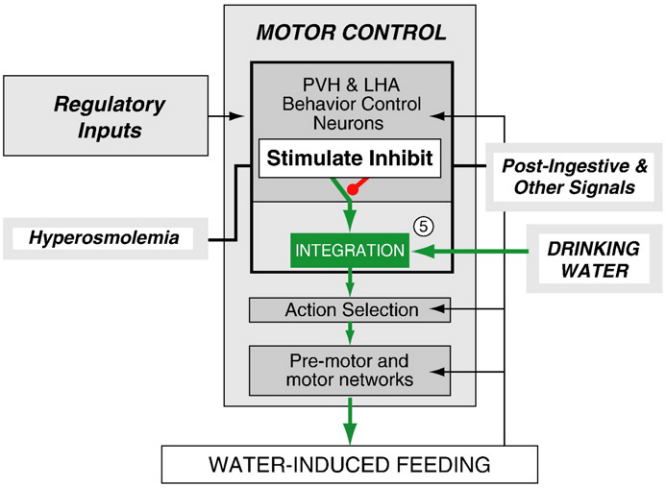

Fig. 5. A schematic representation of the functional networks that interact to generate feeding in dehydrated-anorexic animals after the return of water. Our results suggest a two stage process. First, signals generated by drinking water act within the integration process (5) to quickly stimulate feeding, perhaps by disinhibiting signals from the stimulatory networks. A second, slower process appears to normalize meal patterns as plasma osmolality drops to control values. The networks then return to the state illustrated in Fig. 1 (see text for details).

mechanism involves the sensors in the upper GI tract that not only help mediate the suppression of feeding during dehydration but also contribute, at least in part, to the feeding that follows water intake in water-deprived animals [18]. This GI-mediated mechanism may be similar to that responsible for the rapid suppression of plasma vasopressin secretion that occurs in dehydrated rats with the return of water [30].

A second process involves a slower suppression of activated satiety mechanisms, and is likely driven by the drop is plasma osmolality resulting from drinking water. The presence of a slower suppression is supported by the fact that although meal size in DE-anorexic rats quickly recovers to match that seen in PF rats, DE-anorexic eat fewer meals than PF animals over the following 12 h [29]. Furthermore, the maintenance of hyperosmolemia-dependent inhibition during the initial feeding bout is consistent with our findings that Fos expression in CRH neurons in the LHA remains elevated at least 45 min after the return of water [12], and *Crh* expression in the LHA takes between 5 and 12 h to return to control values once drinking water is re-established [13].

6. Conclusion

The anorexia that mammals develop as a consequence of cellular dehydration is a vital adaptive response that helps limit fluid loss. Using a systems level approach that correlates neural responses with the ongoing sequence of behavioral actions, we have now revealed some of the neural network properties that contribute to the development and reversal of DE-anorexia. A significant component to the expression of DE-anorexia is the fact that meal size rather than meal number is reduced. Indeed, DE-anorexic animals initiate the same number of meals as controls over the course of a day, but these meals are prematurely terminated. A similar response is seen when DE-anorexic animals are injected with NPY into the hypothalamus. These observations focus attention on the increased activity of networks that usually suppress feeding.

On the other hand, the signals that encode negative energy balance generate normal signature responses in the hypothalamus of DE-anorexic animals, demonstrating that anorexia does not arise because of a dysfunctional response to decreasing nutrient intake. The increased activity in the stimulatory networks appear to provide animals with a mechanism to begin feeding again once water becomes available; a response which is remarkably rapid and robust. We propose that signals derived from drinking water can disinhibit activated stimulatory networks to rapidly stimulate feeding. However, more detailed meal pattern analyses reveal the presence of other inhibitory mechanisms that take longer to disengage.

Collectively these results underscore the complex and varied neural network interactions that provide animals with the ability to adapt their feeding behaviors to deal with the many pressures imposed by the environment.

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