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Published in:
 Physiology & Behavior

DOI:
[10.1016/j.physbeh.2010.03.016](https://doi.org/10.1016/j.physbeh.2010.03.016)

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Document Version
 Publisher's PDF, also known as Version of record

Publication date:
 2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Scheurink, A. J. W., Boersma, G. J., Nergårdh, R., Sodersten, P., Nergårdh, R., & Södersten, P. (2010). Neurobiology of hyperactivity and reward: Agreeable restlessness in Anorexia Nervosa. *Physiology & Behavior*, 100(5), 490-495. <https://doi.org/10.1016/j.physbeh.2010.03.016>

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Neurobiology of hyperactivity and reward: Agreeable restlessness in Anorexia Nervosa

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ARTICLE INFO

Article history:

Received 15 January 2010

Accepted 18 March 2010

Keywords:

Dopamine

Orexin

Food anticipatory activity

Activity based anorexia

ABSTRACT

Restricted food intake is associated with increased physical activity, very likely an evolutionary advantage, initially both functional and rewarding. The hyperactivity of patients with Anorexia Nervosa, however, is a main problem for recovery. This seemingly paradoxical reward of hyperactivity in Anorexia Nervosa is one of the main aspects in our framework for the neurobiological changes that may underlie the development of the disorder. Here, we focus on the neurobiological basis of hyperactivity and reward in both animals and humans suggesting that the mesolimbic dopamine and hypothalamic orexin neurons play central roles.

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.

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1. Food intake and physical activity: an evolutionary perspective

Ever since Neel [1] proposed the existence of “thrifty genes” any publication on the evolutionary perspective on (over)feeding and body weight control emphasizes the importance of the relative unpredictable periods of feast and famine during evolution in man (e.g., [2]). This evolutionary pressure led to overfeeding when food was abundant and increased efficiency in the storage of energy substrates, particularly fat [1]. These changes were beneficial for survival, and so the human brain adapted: it made overconsumption of high fat and high caloric food rewarding and it slowly shifted the upper level for homeostatic regulation of body weight to a higher value [3].

It is important to note that the shift to increased energy intake in times of plenty is generally accompanied with a simultaneous reduction in physical activity [4]. Physical inactivity significantly reduces energy expenditure and is as important as increased food intake for storage of energy when food is in supply. Thus, there were at least three important factors that have emerged during evolution in man in times of plenty: people continuously overeat, are physically inactive and store energy very efficiently. Together, these factors offer the perhaps simplest, least redundant explanation of the current epidemic of obesity.

However, with all the current emphasis on the obesity problem, one seems to forget that shortage of food, rather than abundance, is the main evolutionary pressure under which human biology has evolved [5]. One should therefore appreciate the adaptations that

made survival possible during the inevitable periods of famine. The physiological responses to starvation are well described: lower body temperature, reduced heart rate, low body fat percentage and reduced levels of leptin and insulin combined with an increased sensitivity for these hormonal factors as are some of the metabolic effects [6,7]. The behavioral responses are less well documented. Probably the most interesting adaptation is that shortage of food is generally accompanied with an increased capacity for intermittent high levels of physical activity [8]. Increased physical activity was crucial for the original hunters and gatherers to survive in times of famine. But the importance of increased physical activity in times of restricted food access is also illustrated in more contemporary studies on the life of Australian Aboriginals in their natural environment and the reports from the Dutch Hunger Winter [5]. Since periods of famine were probably more frequent than times of plenty [9] one may even argue that a low body weight combined with a high level of physical activity is the original and therefore the real human homeostatic phenotype [5]. Hence, we need to acknowledge that restricted availability of food is associated with increased physical activity, the obvious basis for foraging for food; an efficient foraging strategy is long recognized as a main evolutionary advantage [10].

Thus, from an evolutionary perspective it may be concluded that there is a direct and functional relationship between food availability and physical activity: increased food intake is associated with reduced physical activity whereas restricted access to food will lead to hyperactivity.

2. Activity-based anorexia and food anticipatory activity

Hyperactivity in periods of reduced food availability is not unique for humans. Curt Richter, the famous American psychobiologist already

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found that if food is served for a limited period of time the meal is preceded by an increase in physical activity [11]. This phenomenon is referred to as food anticipatory activity (FAA). The biological explanation for the fact that meals are preceded by FAA is similar to the abovementioned evolutionary approach to human hyperactivity in starvation: animals need to be active in search for more food if the supply of food is limited (as is commonly the case in the natural habitat). Interestingly, a pioneer of the study of patients with Anorexia Nervosa (AN) pointed out that they too show FAA [12].

Food anticipatory activity, noted already by Skinner [13] is an extremely powerful phenomenon in many animals including rats (for a review see [14]). If rats are allowed to eat for only 1 h a day and also given the opportunity to run in a running wheel, they will gradually increase their daily running activity (Fig. 1). In this condition they will run themselves to death within 5–7 days [15]. This exaggerated hyperactivity during restricted food access is known as *activity-based anorexia* (ABA). Phenomena such as ABA and FAA (Fig. 2) are most prominent in rats with access to a running wheel but also occur in food restricted rats housed in very large cages with several play objects or groups of food restricted rats housed together in a large colony cage (Boersma and Scheurink, unpubl data).

3. Hyperactivity in Anorexia Nervosa

Reduced food intake combined with enhanced physical activity is prominent in patients with AN as was noted already 136 years ago [16] and has since been confirmed [17,18]. An illustration of hyperactivity in AN is presented in Fig. 3. We quantified the average activity of the patients with a Mini-Logger® (Mini-Mitter Co, Inc, North Bend Oregon) over a period of 7 days. Fig. 3 shows the 24 hour activity patterns of two AN patients. For comparison the activity patterns of one obese patient who followed a special exercise program from 8 to 12 AM is also presented in this figure. While measuring physical activity, the meal schedules of the patients were also monitored. Fig. 4 combines the meal schedule of one of the patients with her activity score during one of the recording days. Note the peaks of activity in the periods directly preceding a meal and the remarkable resemblance with the FAA patterns in the ABA model, in accordance with the clinical observations made by Bruch [12].

Hyperactivity is nowadays demonstrated in many AN patients and has been accepted as a key characteristic of the disorder. Hence, the original, qualitative clinical observation made by Gull [16] has been reaffirmed; Gull noticed that self-starving girls were not only emaciated and hypothermic but also restless and hyperactive. These were incisive clinical observations and Gull went on to note firstly, that the hyperactivity was very difficult to control and secondly, that it appeared to be agreeable and rewarding for the patients. In our view, Gull's

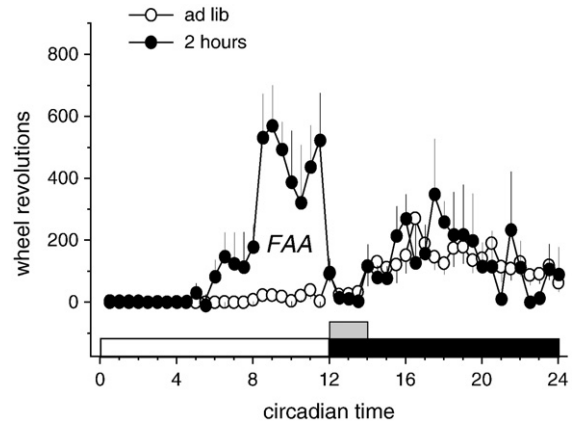


Fig. 2. Food anticipatory activity (FAA): if food is served for a limited period of time, the meal (provided from CT10 to CT12) is preceded by an increase in running activity (expressed as wheel revolutions per 30 min).

agreeable restlessness is directly comparable to the rewarding properties of increased physical activity in the hunters and gatherers and all other human and animal models combining restricted food intake and hyperactivity. Recently, this hypothesis has received further support [19,20].

4. Physical activity and reward

From the paragraphs above, one may conclude that an increase in physical activity during food restriction may initially be functional and, therefore, agreeable or rewarding. But it is important to realize that physical activity, running in particular, by itself is rewarding and may even be addictive; e.g., by causing release of endogenous opioid peptides in the brain [21]. Just as in wheel running rats, regular distance runners report feelings of euphoria after a strenuous bout of exercise (runner's high), the need to increase the running distance to achieve feelings of well-being (tolerance), difficulties in job performance and social interactions (addiction) and symptoms of withdrawal, including depression, irritability, and anxiety, when prohibited from running; (withdrawal)[22–26].

Several studies provide further evidence for the rewarding properties of running and/or hyperactivity. In a T-maze test, which determines the preference of the individual, rats were found to choose the arm of the maze that gave them access to a running wheel [27]. Likewise, rats showed a clear place preference for an environment that was presented

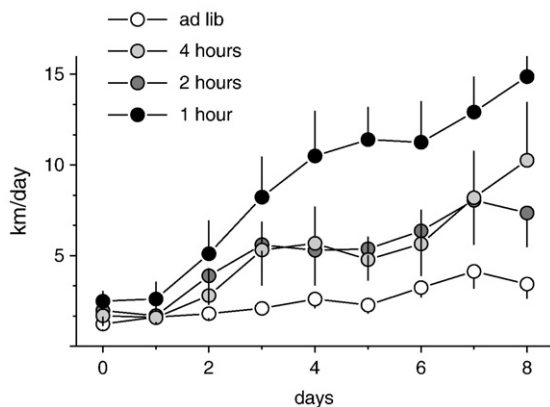


Fig. 1. Restricted access to food for 1, 2 or 4 h per day leads to a dose-dependent increase in running activity. Ad lib rats serve as controls.

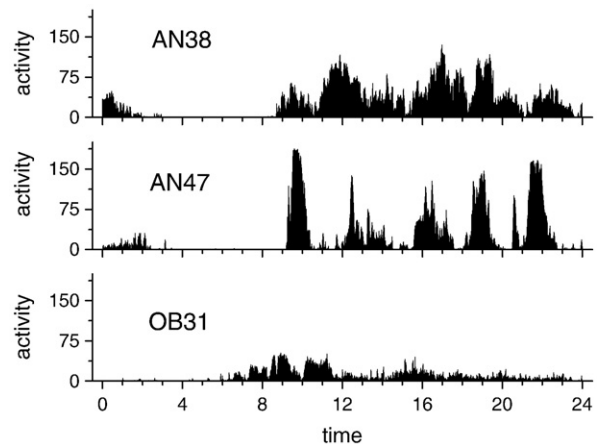


Fig. 3. Average 24 hour activity in two Anorexia Nervosa (AN) patients and one obese (OB) individual. Note that the obese individual followed a special exercise program between 8:30 and 11:30 AM.

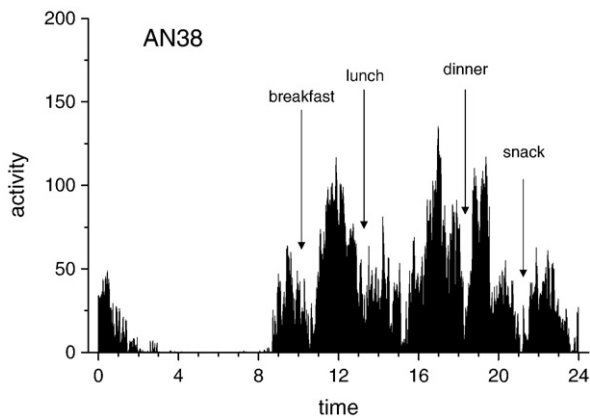


Fig. 4. Meal schedule and activity patterns of one AN patient. Note the remarkable resemblance with the FAA in the ABA model.

immediately after wheel access [28]. The most convincing observation though is that rats are willing to press a lever to gain access to a running wheel [29–31]. Interestingly, rats not only pressed the lever on a standard fixed-interval, but were also motivated to learn intricate variable ratio's to gain access to the running wheel [32], to a similar extent as observed in rats lever pressing to gain access to drugs of abuse.

Another line of evidence for the rewarding properties of physical activity comes from mechanisms involved in reward. Generally, drugs of abuse (as well as food) are thought to owe their rewarding characteristics to activation of the mesolimbic dopamine system [33]. The mesolimbic system consists of a dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), and the NAc shell has projections mainly to limbic structures including the lateral hypothalamus and the cortex [34–36]. There is growing evidence that running and drugs of abuse activate overlapping neural systems [33,37–40]. Chaouloff and colleagues [41] showed that physical activity activates the mesolimbic dopamine system. Furthermore, both wheel running and drugs of abuse increase dopamine release within the reward pathways, augment central dopamine levels, and alter dopamine binding [42,43]. Additionally, like drugs of abuse, running wheel changes the expression of receptors specific to the mesolimbic and mesostriatal dopamine system; activity increases levels of Δ FosB within the NAc, while overexpression of Δ FosB in striatal dynorphin neurons enhances both running and drug self-administration [40,44].

The final evidence for similar rewarding properties of physical activity and drugs of abuse can be found in the interactions between these two factors. Drugs of abuse are known to interact in two different ways. First, two drugs of abuse can be interchanged with each other. When a second drug of abuse is made available this can replace the use of the initial drug (reviewed in [45]). Similar to drugs of abuse, wheel running attenuated self administration opiates, alcohol and psychomotor stimulants (e.g. amphetamine and cocaine) [46–50]. Secondly, addiction to one drug generally reinforces the use of a second drug. Cocaine administration, for example enhances addictive behavior for ethanol. Werme and colleagues [44] have shown that wheel running reinforced ethanol addiction in a similar manner as does cocaine administration. Again, these studies confirm a rewarding, and possibly even addictive properties of physical activity, in particular running. The recent neuroimaging evidence of activation of the VTA-NAc dopamine neurons in AN-patients is consistent with this evidence [19].

5. Addicted to hyperactivity: a theoretical framework

It is generally assumed that AN patients initially increase their physical activity as a means to reduce their weight. We believe,

however, that, as dieting progresses, AN patients become addicted to the physical activity [20]. Indeed, individuals with eating disorders, who exercise, report that it is difficult to refrain from exercise despite many adverse physical consequences (e.g., an unhealthy decrease in body weight, decreased bone density, stress fractures). Additionally, symptoms reminiscent of drug withdrawal, including anxiety, depression, and irritability often develop when these individuals are unable to exercise [22–24]. Finally, there is evidence that drug abuse has increased among eating disorder patients, although more often among bulimics than among anorexics [51,52], offering perhaps further evidence of a common neurobiological engagement in these two conditions.

Reduced food intake and high physical activity are still being recognized as the two main risk factors of AN [5,53]. We already pointed out that the physical activity during food restriction is functional, rewarding and potentially addictive. Likewise, it has been suggested that losing weight can also be enjoyable, pleasurable or rewarding, particular to a woman [54]. In fact, any clinician familiar with eating disorder patients have heard her/his patients say how good it felt to eat less and move more. These observations support the idea that both risk factors for AN may activate the reward pathways in the brain [53]. Therefore, we hypothesize that the dopaminergic reward system plays a crucial role in the development of AN. Supporting evidence for this possibility comes from studies describing associations between dopamine 2 receptor polymorphism and AN; although this evidence is rather indirect and the associated cause-effect relationship is unclear [55,56].

Based on these assumptions, we defined the following theoretical framework for the neurobiological mechanisms underlying the development of AN. The condition develops because it is rewarding to eat less food and be active (dopamine-reward system). The reward systems involved extend from the mesencephalic dopamine cell bodies in the VTA to the NAc in the ventral striatum and forebrain [5]. But the two risk factors for AN, physical activity and a reduction of food intake, do not only activate brain systems of reward but also those concerned with attention, i.e., the capacity to attend to sensory stimuli [5]. In the brain, the attention system is mainly represented by noradrenalin-containing cell bodies in the locus coeruleus in the brainstem that project towards many forebrain regions [5]. As body weight gradually decreases and physical activity increases, the experience of reward is replaced by an urge to be active to avoid the symptoms of abstinence, just as how any other dependence develops [20]. We have suggested that in this situation, anorexic behavior is maintained because it is conditioned to the stimuli that originally provided the reward (noradrenalin-attention system). In other words, the combination of increased reward and attention may create an optimal situation for learning. Thus, it might be initially rewarding to diet and to be active and, at the same time, the patient learns what stimuli provide the reward. The behavior of the anorexic patient is then maintained by conditioning to these stimuli. For an in depth overview of the neural networks engaged in cue-controlled eating, reward and attention we refer to a previous review by Södersten et al. [5].

6. The neurobiology of ABA

Human studies may only offer indirect information on the neurobiological engagement in the hyperactivity of AN; an animal model is required. Whilst there is no direct evidence that healthy animals display self-starvation in the same manner as AN patients, the ABA-paradigm (restricted access to food combined with the availability of a running wheel) comes very close to the hyperactivity in AN (see [57] for a discussion of the many similarities and few differences between the two). Thus, the ABA-model meets many of the validity criteria for AN, in particular the hyperactivity under starvation conditions. ABA-rats even display self-starvation if the period of food restriction is prolonged [58].

7. Dopamine

Many recent studies on hyperactivity in the ABA model focus on dopamine signaling within the mesolimbic reward mechanism of the brain. Administration of a non-selective dopamine antagonists as well as lesions of dopamine neurons in the NAc decreased the FAA [59,60], there are, however, conflicting data [61]. In addition, dopamine depletion as well as dopamine receptor blockade, either D1 or D2 reduced food associated activity as well [62,63]. Whilst measurements of dopamine release in the NAc by means of microdialysis failed to show an increase during FAA in ABA rats [60], indirect evidence for an involvement of the mesolimbic reward pathways in the hyperactivity in ABA derives from studies in which rats exposed to the ABA paradigm display more withdrawal symptoms after being injected with the opioid antagonist naloxone compared to both active rats without food restriction and inactive rats with food restriction [21,64]. Interestingly, the degree of withdrawal symptoms correlated strongly with the degree of hyperactivity observed [64].

8. Orexin: a neuropeptide involved in food restriction, hyperactivity and reward

The mechanisms through which the activation of the dopaminergic mesolimbic system reinforces running wheel behavior during food restriction (and vice versa) remain partially elusive. We hypothesize that ABA-hyperactivity might be reinforced by an interaction between orexinergic neurons in the lateral hypothalamus and the dopaminergic reward system. Orexin is involved in arousal and food intake processes; activation of orexin receptors leads to an increase in physical activity and, interestingly, orexin is released in response to food restriction [65,66]. By itself, these actions and alterations of hypothalamic orexin makes this neuropeptide of particular interest for studies on starvation-induced hyperactivity. But it has also been documented that the orexin system plays a central role in reward mechanisms and the effects of drug of abuse [67,68]. Hypothalamic

orexin neurons project to the VTA [69–71], and both dopaminergic and non-dopaminergic neurons in the VTA are excited by orexins [72,73]. It has been shown that orexin signaling is involved in cocaine- and morphine-induced hyperlocomotion and place preference through the mesolimbic dopamine system [72,74]. Furthermore orexin deficient mice are less susceptible to develop drug dependence [75] and orexin injection into the VTA can reinstate an extinguished preference for drugs of abuse [76]. Orexin may therefore mediate the rewarding properties of hyperactivity by interacting with the mesolimbic pathway by amplifying dopamine release and providing an incentive for an animal to express previously rewarded running activity.

9. Dopamine–orexin interactions

There are direct interactions between the orexin neurons in the lateral hypothalamus and the dopaminergic mesolimbic system. This connection seems to have a bidirectional character: orexin neurons project to the VTA [35] and via the dopamine 1 receptor orexin neurons are excited by the mesolimbic dopamine system [77]. This bidirectional activation creates a positive feedback loop enhancing initial activation of the reward pathway.

Our own data support these interactions between dopamine and orexin. First, we observed increased orexin mRNA expression in the lateral hypothalamus (LH) in rats displaying ABA (Fig. 5A). Secondly, we were able to attenuate ABA-induced body weight loss by administering a selected orexin 1 receptor antagonist (Fig. 5B). Thirdly, both ABA-induced weight loss and the development of FAA were blocked by administration of a selective dopamine 1 receptor antagonist (Fig. 5C). Fourthly, the over expression of orexin mRNA during ABA was blocked by administering the dopamine 1 receptor antagonist (Fig. 5D). These results support our hypothesis that ABA activates a positive feedback loop between orexin neurons in the LH and the mesolimbic dopamine pathway.

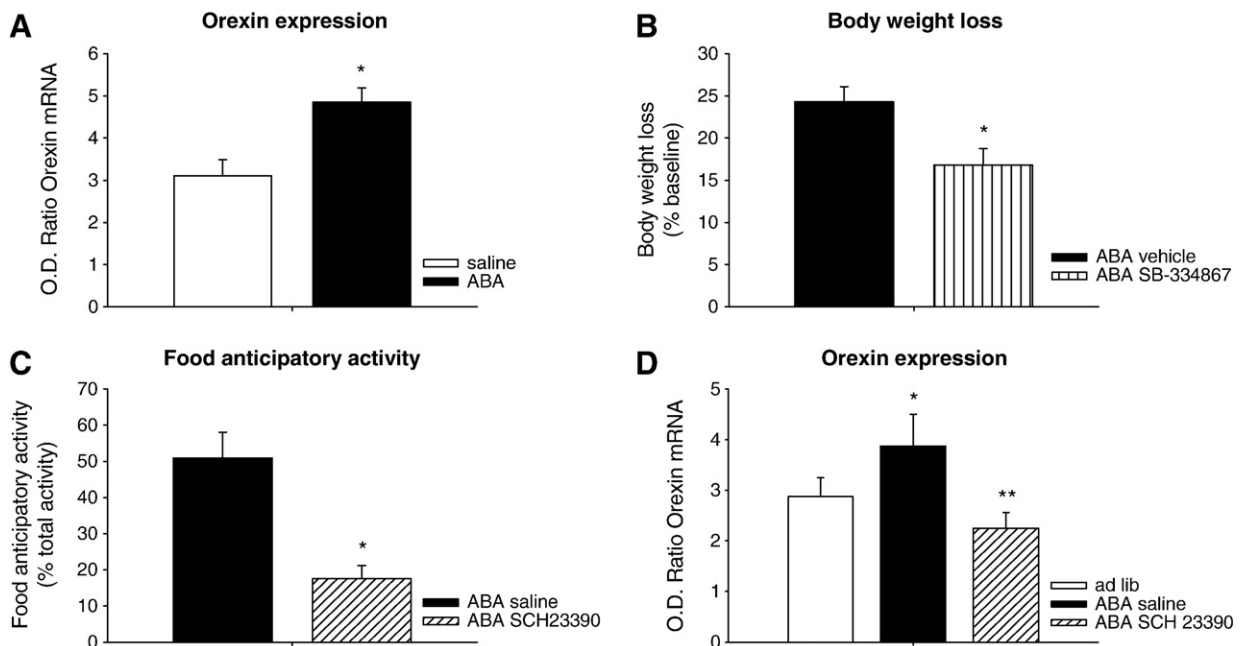


Fig. 5. A: orexin mRNA expression in lateral hypothalamus (LH) in ad lib fed rats (White bars, $n = 6$) and rats expressing activity-based-anorexia (ABA) (Black bars, $n = 6$). B: Body weight gain during the ABA regime of rat treated with either an orexin 1 receptor antagonist (SB-334867, $n = 8$) or vehicle (DMSO, $n = 8$). Body weight loss on day 6 is presented as a percentage of the baseline body weight of the rats on the 8 days prior to the start of the food restriction. C: Food anticipatory activity (expressed as a percentage of total daily activity) on the 6th day of the ABA paradigm in rats treated with saline (Black bars, $n = 8$) or the dopamine 1 receptors antagonist SCH23390 (Diagonally striped bars, $n = 8$). D: orexin mRNA expression in LH in ad lib fed rats (White bars, $n = 5$), in ABA expressing rats treated with saline (Black bars, $n = 5$) and in ABA expressing SCH 23390 treated rats (Diagonally striped bars, $n = 4$). Fig. 5A and D were adapted from the thesis of Ricard Nergårdh [87]. * indicates a significant difference compared to the control group ($p < 0.05$), ** indicates a significant difference compared to the ABA saline group ($p < 0.01$).

10. Reflection

Admittedly, we have mentioned only some selected aspects of starvation-activity neurobiology. Some well known, additional aspects should be added to make this picture less incomplete. Hence, it is long known that the expression of physical activity, particularly in wheel-running models, is controlled by the suprachiasmatic hypothalamic generator of circadian rhythms, with light being a main entrainer of the rhythm [78]. However, it is equally well known that food is a powerful entrainer of activity rhythms [14]. Neuropeptide Y increases in the hypothalamus in association with food deprivation, enhances wheel running and decreases food intake in the ABA-model [57] and has been implicated in non-light entrainment of activity rhythms mediated by a thalamo-suprachiasmatic pathway [79]. Yet, the location of the food-entrainable circadian oscillator has remained elusive. However, it was recently suggested to be located to the ghrelin-producing cells of the stomach [80]. This observation is particularly interesting in the present context because ghrelin, of course, is increased in the starvation of AN as in other kinds of starvation [81]. Just like neuropeptide Y [82], ghrelin has been suggested to play a role in food anticipatory activities [83]. Clearly, the neuroendocrine cascades engaged in human AN and animal ABA are far from a complete description; many exciting discoveries lie ahead.

Finally, a word of reflection might be appropriate. “Reward” and more generally “motivation” is, of course, an intervening construct, not a place in the brain. A founder of behavioral neuroendocrinology felt that “motivation is the phlogiston of psychology” [84]. There is a risk by using intervening constructs and it is therefore not surprising that studies on the neural engagement of “reward” or “pleasure” or even “happiness” engage neurochemical networks beyond mesolimbic dopamine pathways. Behavioral scientists are often best off when behavioral data are combined with as few intervening variables as possible.

11. Conclusion

We tentatively conclude that the hyperactivity of starvation has a biological, evolutionary basis that was initially functional and rewarding; the high physical activity of AN patients is likely an expression of this evolutionarily ancient behavior akin to what Tinbergen referred to as “vacuum activity”, beyond voluntary control and which hampers recovery [85]. The seemingly paradoxical rewarding aspect of the hyperactivity in AN is one of the main aspects in our framework for the neurobiological changes that are associated with the development of AN. This framework was launched to combine experimental behavioral neuroendocrinology with the clinical phenotype of AN [53], and has since then been extended to include more recent information on the neuroendocrine and behavioral characteristics of a low body weight in humans, “the human homeostatic phenotype” [5]. In this paper we have discussed the neurobiology of hyperactivity and reward in AN, in particular the engagement of mesolimbic dopamine reward pathways and hypothalamic orexin neurons.

Whilst it remains to be determined if these new insights can be implemented clinically, our framework has already guided our clinical work; Gull [16] was right in that restriction of patient’s physical activity is a major intervention. Other important interventions include removal of the cues which maintain disordered eating [5], but above all learning normal eating patterns. A randomized controlled trial demonstrated that a combination of these interventions are effective and results in a remission rate of 75% in a large group of patients ($n = 168$) and a relapse rate of only 10% in a year in 83 patient in remission [86]. This outcome is encouraging and we expect further progress as the neurobiology of physical activity and other issues related to the effects of starvation emerges.

Acknowledgements

This review is based on a presentation at the 2009 Annual meeting of the Society for the Study of Ingestive behavior. The authors would like to thank Alan Watts (USC) for organizing the session: “Anorexia: diversity in mechanism and outcome”. In addition, we would like to thank Stefano Guidotti, Ahmed A. Ammar, and Bertil B. Fredholm for their contributions to the experiments displayed in Fig. 5.

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