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Evaluating anhedonia in the activity-based anorexia (ABA) rat model

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ABSTRACT

Patients suffering anorexia nervosa (AN) become anhedonic, in other words, unable or unwilling to derive normal pleasures and avoid rewarding outcomes, most profoundly in food intake. The neurobiological underpinnings of anhedonia are likely to involve mesolimbic reward circuitry. We propose here that this circuitry and its involvement in AN can be investigated using the activity-based anorexia (ABA) rodent model that recapitulates many of the characteristics of the human condition, most notably rapid weight loss. Preference for sweetened water was used to assay hedonic processing in female Sprague-Dawley rats exposed to the ABA protocol, which involves free access to running wheels paired with time-limited access to food. This protocol uncovered a transient anhedonia in only one quarter of cases; however, exposure to running wheels alone was associated with a rapid aversion to sweetened water ($F_{1.833,\ 20.17} = 78.29$, $p < .0001$), and time-limited food access alone did not impact preference ($F_{2.205,\ 24.25} = 0.305$, $p = .761$). High levels of running wheel activity prior to the onset of food restriction increased susceptibility to body weight loss in ABA ($F_{10,196.129} = 2.069$, $p = .029$) and food anticipatory activity predicted subsequent food intake only for rats that were resistant to body weight loss ($r = 0.44$, $p = .001$). These data are inconsistent with the hypothesis that anhedonia underscores the precipitous weight loss in ABA, however, they highlight the predictive nature of hyperactivity in susceptibility to the ABA paradigm. These results will help inform the neurobiological framework of ABA and provide insight into the mechanisms of reward relevant to feeding and weight loss.

1. Introduction

Anorexia Nervosa (AN) is a debilitating psychiatric illness that is characterised by extreme dieting and excessive exercise undertaken to achieve weight loss [1]. AN has underlying neurobiological drivers that contribute to both the onset and maintenance of these behaviours [35], which have been elucidated with functional brain imaging techniques of acutely-ill and weight-recovered AN (REC-AN) patients [34]. REC-AN patients present a valuable opportunity to investigate enduring differences in the neurobiology underpinning the condition that are not compromised by the acute effects of starvation. The most readily observable behavioural feature of AN is excessive exercise, which is a characteristic of the majority (80%; Davis 1997) of AN patients, and normally precedes clinical diagnosis [10, 12, 38]. While excessive exercise itself is not a cause of AN, the progression of the disorder is exacerbated by broad neuroendocrine changes (e.g. changes in the levels of circulating leptin and ghrelin) that promote energy expenditure during the acute stage of the illness [31, 38]. This paradoxical increase in energy expenditure accompanying body weight loss in AN is mirrored in rats that develop “starvation-induced hyperactivity” when placed on a restricted feeding schedule [21, 29].

A key psychological component of AN is anhedonia, whereby patients become unable or unwilling to derive normal pleasures associated with reward. Anhedonia is more prevalent in AN than other eating disorders, and excessive exercisers tend to be more anhedonic than non-exercisers [13]. In addition, REC-AN patients find high energy foods aversive [33], prefer low-calorie over high-calorie foods (the inverse of healthy controls; [9]) and report increased anxiety, as opposed to pleasure or euphoria [54], following eating [35] or amphetamine administration [2]. AN patients are also ascetic in that they are capable of extreme self-control in rejecting or delaying the receipt of reward [14, 56]. Functional imaging studies demonstrate that the neurobiology underlying anhedonia in AN is likely to involve disrupted dopamine (DA) signalling in reward pathways in the brain. For example, compared to healthy controls, REC-AN patients show decreased striatal activity in response to sucrose [61], abnormal striatal activity in behavioural tasks involving reward valuation [14] and increased striatal binding of a competitive D2/D3 radioligand, indicating upregulation of DA receptors or decreased endogenous DA levels [25]. Furthermore, ascetic behaviour likely arises from increased activity in cognitive control networks. For example, during both the anticipation of and after receipt of a reward, REC-AN patients display increased activity in the

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dorsolateral prefrontal cortex (dlPFC), a key region within the cognitive control domain, indicating increased regulatory control over reward-related processing [20]. Moreover, sucrose-invoked activity in the insula, a brain region involved in interoceptive awareness (i.e. recognition of hunger sensations), is decreased in REC-AN patients compared to healthy controls [43, 61] and is not correlated to pleasantness ratings, unlike in control subjects [61]. The prevailing neurobiological view of AN, incorporating these findings, is that decreased activity in mesolimbic reward circuitry and increased activity in prefrontal control circuitry act in combination with disrupted insula signalling to override homeostatic requirements for energy balance, resulting in emaciation in AN.

Given unlimited access to a palatable diet, humans and rodents alike will typically overconsume resulting in weight gain [53], yet AN occurs within the context of abundant and readily accessible highly palatable foods. Thus, anhedonia and asceticism may represent the behavioural manifestation of the underlying neurobiological shift described above [62]. In order to interrogate the behaviours underpinning the development of AN and the neural circuitry subserving them, it is necessary to utilize appropriate animal models. The activity-based anorexia (ABA) rodent model is the most robust and widely used animal model of AN. It is a behavioural model that recapitulates the core features of the human condition, namely extreme and rapid weight loss, excessive exercise and hypothermia [3, 27]. ABA involves voluntary and unhindered access to a running wheel paired with time-restricted access to an unlimited quantity of food. It is important to note that rats with access to a running wheel alone increase their activity over time but compensate for their increased energy expenditure by increasing food intake such that normal body weight gain is maintained [18, 44]. Similarly, rats can readily adapt to food restriction schedules alone, displaying an initial small decrease in body weight which is then maintained by increasing intake when food is available [18, 50, 55]. Paradoxically, when given the combination of wheel access and time-limited food access, rats in the ABA paradigm become markedly hyperactive [27] compared to ad libitum fed rats with running wheel access [44] and eat comparable amounts [18, 44] or less [28, 50, 55] than sedentary rats on the same food restriction schedule. This results in rapid and severe body weight loss (> 25% in a week) in the majority of animals exposed to the paradigm [18, 19, 23].

To date, the most effective avenue for prevention and treatment of ABA has been targeting reward-related mechanisms. Pharmacological dopamine antagonism [36, 49, 58], provision of a highly palatable diet [6, 59] and THC administration [59] all prevent ABA-associated body weight loss. The mesolimbic reward network is largely mediated by dopamine signalling, therefore interventions that increase the hedonic or rewarding properties of food likely act via dopamine-mediated mechanisms [5]. Indeed, we have recently demonstrated that direct chemogenetic activation of the mesolimbic reward pathway prevents and rescues the characteristic body weight “free fall” that accompanies ABA [23]. While it is clear that patients suffering from AN display anhedonia, it remains to be determined whether anhedonia is a feature of the ABA model, and if so, whether it underscores the rapid body weight loss that typifies ABA. The gold-standard test for hedonia in rats is the two-bottle preference test; in which rats choose to drink either regular or sweetened water and the proportion of sweetened water consumed gives an index of hedonia [15]. Therefore, the present studies were performed to determine 1) whether anhedonia is associated with body weight loss in rats exposed to the ABA paradigm and 2) whether a disruption in hedonic processing in ABA is reversed with body weight recovery.

2. Materials and methods

2.1. Animals

Female Sprague-Dawley rats for these studies were sourced from the Animal Resources Centre (ARC; Canning Vale, WA Australia) with initial body weights between 140 and 160 g. All experimental procedures were approved by the Monash Animal Resource Platform Ethics Committee. A singly housed male rat was present in all experimental rooms to synchronise the estrous cycles of the female rats (known at the Whitten effect; [32]).

2.2. Baseline preference for sweetened water

To determine baseline preference for sweetened water, rats ($n = 27$) were individually housed in standard opaque polypropylene cages with wire lids in a temperature (27 °C) and humidity (21%) controlled room with a 12 h light-dark cycle (lights on 0700 h). Rats had ad libitum access to food and water for the duration of the experiment. Two-bottle preference tests were conducted twice daily (1100–1230 h and 1430–1600 h), in which rats ($n = 12$) chose to drink from a bottle containing tap water or a bottle containing nutritive or non-nutritive sweetened water of varying concentrations diluted in tap water (Sucrose 0.5–6%; Saccharin 0.0025–0.10%). The location (left/right) of the sweetened water was alternated between rats for each test and within rats for consecutive tests to eliminate any side preferences. Each rat received every concentration once and tests were considered reliable and included in analyses if ≥0.25 ml of the sweetened water was consumed. Preference in two-bottle tests was calculated as: sweetened water intake/(total water intake)*100. Three-bottle preference tests were also conducted in a separate cohort of rats ($n = 15$) between 1100 h–1230 h on three non-consecutive days. The three bottles contained tap water, 1.5% sucrose or 0.02% saccharin. Preference for each solution was calculated as a percentage of total fluid consumed, e.g. 1.5% sucrose intake/(total water intake)*100.

2.3. The ABA paradigm

The ABA paradigm utilised in these studies involved unhindered access to running wheels and time-limited access to food (90 min at the onset of the dark phase). Rats were housed individually in transparent activity wheel and living chambers (Lafayette Instruments, IN, USA; model 80859) lined with dust-free woodchips in a temperature (22–24 °C) and humidity (30–50%) controlled room under a 12 h light/dark cycle (lights off at 1400 h). Rats were always allowed to habituate to the running wheels and light cycle for 11 days prior to the onset of food restriction. ABA was terminated by return to full food access when rats reached < 80% of baseline body weight, or on the second day of spontaneous weight gain.

2.4. Running wheel activity

Each running wheel was connected to an Activity Wheel Counter (Lafayette Instruments, IN, USA) mounted on each cage which was connected by USB interface to a computer running the Activity Wheel Software (Lafayette instruments). Running wheel data were recorded at 10 min intervals for duration of the experiments, whereby one count constitutes one wheel revolution. Daily running wheel activity (RWA) comprised total counts over 24 h beginning/ending at 1400 h (e.g. daily RWA graphed at X = day 2 is total RWA between 1400 h day 2 and 1400 h day 3). RWA in the hour before feeding 1300–1400 h represented the window of food anticipatory activity (FAA). However, in order to account for individual differences in overall activity levels, an adjusted measure of FAA for each day was calculated by evaluating RWA between 1300 and 1400 h as a percentage of total daily RWA.

2.5. Preference for sweetened water during running wheel activity

In order to assess the independent effects of running wheel activity and food restriction on saccharin preference, a series of two-bottle preference tests were conducted using 0.02% saccharin. Rats ($n = 12$)