The hormonal signature of energy deficit: Increasing the value of food reward

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ABSTRACT

Energy deficit is characterised by high ghrelin levels, and low leptin and insulin levels and we suggest that this provides a metabolic signature sensed by the brain to increase motivated behaviour to obtain food. We believe that the hormonal profile of negative energy balance serves to increase the incentive salience (or the value) of a food reinforcer, which in turn leads to increased motivation to obtain this reinforcer. These processes are mediated by a number of alterations in the mesolimbic dopamine system which serves to increase dopamine availability in the forebrain during energy deficit. The currently available evidence suggests that changes in motivational state, rather than hedonic enjoyment of taste, are primarily affected by reduced energy availability. This review aims to clarify the term ‘reward’ in the metabolic literature and promote more focused discussion in future studies.

Keywords  Reward; Motivation; Dopamine; Feeding; Behaviour; Ghrelin

1. INTRODUCTION

1.1. Defining ‘reward’

The concept of reward is applied widely but is often poorly defined [1], and these problems with labelling extend into the literature around food reward [2]. The scientific term ‘reward’ essentially has three possible meanings as outlined by Sanchis-Segura and Spangelo [3]. It can describe stimuli with a desirable outcome, as the term is usually applied in a lay sense. This is also known as a reinforcer. It can describe the acquisition of a learned response, which earns a positive outcome, also known as contingency learning or positive reinforcement. Finally, it can refer to an inferred internal pleasurable or hedonic state, which occurs once the reward has been obtained or consumed [3]. The argument could be made that these are all part of a bigger picture of an overarching ‘reward pathway’, but the overlap in terminology can lead to confusion and errors in analysis. Certainly, the role that mesolimbic dopamine plays in motivational processes is more complex and nuanced than is often credited in the literature, and the blanket term ‘reward pathway’ is somewhat misleading [1]. This review will endeavour to use the term ‘reinforcer’, ‘positive reinforcement’ and ‘hedonic state’ as they are discussed above to avoid confusion with the term ‘reward’.

1.2. Computing value: incentive salience

The core role of mesolimbic dopamine in eating deals with the motivational aspects of food-seeking rather than the hedonic value of consumption or the ability to learn associations between stimulus and outcome. Mice completely lacking dopaminergic signalling (dopamine deficient, DD, mice) still show a preference for sucrose solution over water [4] and remember the location of treats in a T maze [5], indicating that dopamine is not critical for these processes. In both these studies the DD mice showed deficits in how much work they were willing to do to obtain the reward, also known as wanting or appetitive drive. The idea that this aspect of reward processing is most affected by dopaminergic signalling has been discussed at length by others [6,7], so suffice to say here it is becoming more clear that the role of mesolimbic dopamine, broadly speaking, is to encode the process by which an animal assesses the value of the reinforcer against the cost of obtaining it. The value of a reinforcer is not a static representation, and can be influenced by a number of factors such as the internal state of the animal. This concept of the internal representation of the value of a reinforcer at this moment in time is known as ‘incentive salience’ [6]. There are a number of studies that document how changes in physiological need lead to changes in incentive salience of a reinforcer, or how valuable a reinforcer is perceived to be. Under normal circumstances rats do not enjoy a saline solution, but under conditions of experimentally-induced sodium depletion they experience a neuronal response similar to that of ingesting sucrose [8]. Similarly, when monkeys are water deprived their willingness to work for a water reinforcer correlates with the osmolality of their blood, with the animals becoming disinterested in working for a water reinforcer as their blood osmolality approaches normal [9]. These examples highlight the way the incentive salience (or perceived value) of a reinforcer can be acutely recomputed de novo with each presentation of that reinforcer [6], and show that the value ascribed is dependent on physiological need. In both

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these examples, one suggested driver for the shift in the incentive salience of the reinforcer offered is blood osmolality – changes that are sensed by the brain and then produce goal directed behaviour to reinstate appropriate blood solute levels.

1.3. Hunger as an amplifier of incentive salience
This idea that changes in internal environment can be sensed and can influence the value of a reinforcer clearly holds much relevance to regulation of feeding, as organisms have been eating for almost as long as they have been maintaining fluid balance. Negative energy balance is characterised by low levels of plasma leptin, insulin and glucose and high levels of plasma ghrelin and free fatty acids. This humoral state signals to the brain a net energy deficit, which sets off a number of adaptive strategies for regaining neutral or positive energy balance.

Some of the more complex behavioural outcomes of this humoral milieu involve changes to motivation and incentive salience of reinforcers, particularly, although surprisingly not exclusively, food reinforcers.

In flavour preference paradigms where rats are given a preferred reinforcer, such as a sucrose solution, paired with particular flavour, such as grape, they quickly come to prefer grape flavour compared to another flavour which had been paired with water. This is true for both caloric reinforcers such as sucrose and ethanol, and non-caloric ones such as saccharine or caffeine [10]. When hungry, rats show an increased preference for those flavours previously paired with reinforcers containing calories (ethanol, sucrose) while no greater preference is observed with flavours that were previously paired with non-nutritive reinforcers such as saccharine or caffeine [10,11]. This indicates that the physiological state of negative energy balance increases the incentive salience of presumed caloric content of a flavour previously paired with calories. This concept is further supported by evidence that satiety signals – hormones that when endogenously released signal replete energy stores – suppress intake of calorie-paired flavours. The exogenous administration of the gut hormone cholecystokinin (CCK) robustly suppresses feeding in hungry animals, and similarly suppresses consumption of a previously ethanol-paired flavour in hungry rats [12]. This kind of motivational manipulation by humoral hunger and satiety signals has been shown in a range of behavioural paradigms and with a number of hormones. Indeed, this supports the idea that the brain senses a ‘blueprint’ of energy deficit or surplus from the blood, which then informs the organism of the value a food reinforcer by altering motivation or drive.

Studies looking at how food deprivation can shift motivational state offer a basis for trying to uncover the signalling mechanism that causes these shifts in motivation. Fasting decreases both the activity and mRNA expression of the dopamine transporter (DAT) [13], and chronic food restriction increases binding at the D2 receptor [14], supporting the idea that increased dopaminergic signalling is important in the biological response to a fast. A better understanding of the pathways by which metabolic need gets translated into focused, motivated, food seeking behaviour is developing; however, there is still much to be learned. This review will focus on important humoral factors that signal nutrient availability to the brain: insulin, leptin, and ghrelin, in an effort to examine how hypothalamic nutrient sensing mechanisms influence incentive salience and motivational drive under different metabolic states.

2. GHRELIN

Ghrelin plays a broad role in protecting the organism from the consequences of negative energy balance, such as maintaining blood glucose levels during starvation [15,16], as well promoting feeding through a number of pathways. It is well documented that circulating ghrelin acts on agouti regulated peptide/neuropeptide Y (AgRP/NPY)-expressing neurons in the arcuate nucleus (ARC) of the hypothalamus to promote feeding, an effect that is largely considered a homoeostatic response to decreased nutrient availability. Ghrelin’s ability to promote feeding extends to actions on extrahypothalamic pathways, and recent evidence suggests that high ghrelin levels may be a primary driver to alter the incentive salience of food, and thus the motivation to work toward reinforcers, in response to a high metabolic need for food.

Ghrelin given to rats either centrally or peripherally increases their motivation to work for a palatable food reinforcer in a bar press task, meaning that the rats are willing to work harder for longer to obtain the sucrose reinforcer [17,18]. However, similar administration of ghrelin did not affect the lick rate and/or lick rate interval of a sucrose solution. As an increase in lick rate and a decrease in the intervals between lick bouts indicates increased hedonic enjoyment of consumption [18], these results suggest ghrelin does not affect the hedonic experience of consumption.

The ghrelin-induced increase in the lever pressing task is blocked by dopamine D1 receptor antagonists while the same treatment does not alter lick architecture, in line with the known properties of dopamine to promote motivation rather than hedonic states [18]. It also suggests that the value the animal places on a caloric reinforcer is under the influence of ghrelin signalling, indicating that ghrelin may indeed mediate shifts in incentive salience of calories. Others have previously shown that ghrelin promotes consumption of calorically dense foods over palatable foods, and come to the conclusion that ghrelin is not promoting ‘reward’ but rather signalling information on energy density of food [19], fitting with the idea that ghrelin is important in determining the value of a calorie at the moment of ingestion.

Others have suggested a motivational role for ghrelin [20] on the basis of the observation that ghrelin administration into the third ventricle directly increases locomotor activity and dopamine overflow in the nucleus accumbens (NAC). This observation that locomotor activity is increased following ghrelin administration disagrees with previous findings showing that ICV ghrelin decreases locomotor activity [21], however as Jerthag et al. point out a fundamental difference between these two studies is the presence of food when ghrelin-elicted locomotor activity was assessed. When food is present, there is no locomotor response to ghrelin, while in the absence of food locomotor activity increases robustly. More recent studies demonstrated that direct activation of the canonical target neuronal population of ghrelin, arcuate AgRP/NPY neurons, shows the same pattern. Using DREADD technology to acutely activate NPY/AgRP neurons significantly increases locomotor activity in the absence of food, but no change is observed when food is present [22]. Of particular interest to this review, the same paper showed direct activation of the NPY/AgRP neurons significantly increased the breakpoint in a nose poke task to obtain a food reinforcer, showing that the mice had increased motivation to work for food. Importantly, the acute increase in NPY/AgRP neural activity elevated breakpoint to that seen in fasted mice. As NPY/AgRP neurons are more active under negative energy balance [15,23] this suggests that NPY/AgRP neurons are a key target population to connect metabolic status with the incentive salience of food. The increased locomotor activity is interpreted as food-seeking behaviour, as this only happens in the absence of food. Two classical side effects of increased dopamine levels are altered locomotor activity, and increased motivated responding...
so it seems entirely possible that ghrelin, acting through NPY/AgRP neurons, increases mesolimbic dopamine levels thereby altering the incentive salience of food. NPY/AgRP neurons signal using two separate neuropeptides, AgRP and NPY, and use GABA as their neurotransmitter [26]. These three signalling pathways are all sensitive to ghrelin, and work to promote feeding through a complex, distributed network of downstream targets [27–29].

Administration of exogenous AgRP promotes behaviours associated with fat consumption, at the expense of those associated with sugar consumption. Centrally administered AgRP promotes responding for a fat reinforcer in preference to a sucrose one, a reversal of the preference shown by saline-treated rats [30]. Moreover, treatment with AgRP during conditioning period blocks formation of a conditioned place preference for sucrose, but not pelleted high fat diet [31]. Others show that AgRP administration promotes consumption of chow in preference to even relatively concentrated sucrose solutions [32], suggesting it directs consumptive behaviour toward fats or fat to carbohydrate ratio – cues that may indicate greater caloric density. In contrast to these effects of AgRP, ghrelin increases responding for a sucrose reinforcer [17,33], an effect dependent on NPY signalling and opioid neuropeptide transmission in the VTA [33]. Interestingly, opioid receptor antagonist block the increase in chow consumption seen with AgRP administration [32,34], although the specific brain regions involved in this have not been described. Recent evidence describes a clear role for kappa opioid receptor (KOR) involvement in the hypothalamus-mediated effects of ghrelin-induced feeding, rather than mesolimbic mediated processes [35]. Complete suppression of AgRP-induced feeding is seen with subthreshold doses of combined selective KOR and mu opioid receptor (MOR) antagonists [34], suggesting that multiple, overlapping opioid driven circuits regulate downstream effects of ghrelin and NPY/AgRP neuronal signalling.

Recent studies demonstrate that NPY/AgRP neurons innervate the ventral tegmental area (VTA) and directly modulate the dopaminergic neurons via GABAergic signalling [36]. VTA dopamine neurons terminate in a number of forebrain areas and contribute to a range of behaviours and processes. Somewhat counterintuitively, lowering NPY/AgRP neuronal activity using SIRT1 deletion reduced inhibitory control over VTA dopaminergic neurons, meaning that NPY/AgRP neurons apparently exhibit tonic inhibition on this population. NPY/AgRP neurons project extensively throughout the brain [37], and likely affect multiple end processes. GABAergic inhibition from this population onto the parabrachial nucleus (PBN) is critical for feeding behaviour and it is not surprising that ablation/suppression of NPY/AgRP neurons would similarly lead to disinhibition in both populations. The NPY/AgRP system is extremely plastic, as ablation of this population in adulthood results in death by starvation [38,39], however neonatal ablation [39], or germline deletion [40] are extremely well tolerated. Given this, congenital suppression of NPY/AgRP signalling after SIRT1 deletion in these neurons may increase dopaminergic tone as a compensatory mechanism for reduced drive to eat.

The ghrelin receptor (growth hormone secretagogue receptor; GHSR) is found throughout the brain. In addition to being present on NPY/AgRP neurons, it is co-expressed with dopamine D1 receptors in a number of cell populations and the two receptors appear to have functional interaction, at least in vitro [41]. A number of sites within the reward pathway are sensitive to ghrelin administration with both intra-VTA and NAc ghrelin inducing feeding behaviour [42]. In a number of behavioural paradigms ghrelin has reinforcing effects. Ghrelin increases the conditioned place preference for chambers paired with palatable food in the conditioned place preference tests, and suppression of ghrelin signalling in GHSR1a knockout mice attenuates the formation of a preference [43]. Ghrelin also increases breakpoint in progressive ratio tasks, where satiated mice treated with ghrelin show increased motivation to respond for a high fat food pellet. This effect appears to require orexin signalling, as it is absent in orexin-deficient mice [43], however the GHSR1a mRNA is not present in the lateral hypothalamus where the orexin neurons are situated [44,45], suggesting that ghrelin affects these neurons via an indirect pathway. Indeed, orexin-containing neurons receive dense NPY/AgRP projections from the ARC [46] and are extremely sensitive to AgRP [47], so this action of ghrelin presumably acts via an AgRP/NPY neuronal circuit.

The VTA is directly sensitive to ghrelin with direct injection of ghrelin into the VTA increasing feeding, and peripheral ghrelin injection increasing dopamine turnover in the ventral striatum [48]. Ghrelin injected into the VTA results in increased motivated responding to a food reinforcer [49], indicating that circulating ghrelin impacts motivational response through direct action in the VTA. Recently, this has been demonstrated to be dependent on signalling via D1 and D2 receptors in the nucleus accumbens (NAc), where pharmacological blockade of these receptors attenuates lever pressing, but not chow intake following VTA ghrelin administration [50]. This argues for divergent ghrelin-sensitive neurocircuity originating in the VTA, which differentially promotes feeding and motivated responding.

If food is present and animals are freely consuming it, there is no way to separate out the various drivers of that consumption. It may be hedonic, it may be motivational, and it may be ‘homeostatic’ hunger drive. It is only through creating situations where these individual components can be measured that we can gauge their contribution to the overall effect of increased feeding. Ghrelin clearly plays a role in multiple aspects of ingestive behaviour [51] however the evidence does support a strong role for motivational processes in its orexigenic effects, driven by altered valuation or increased incentive salience of food reinforcers. We suggest the canonical homeostatic pathway of ghrelin acting via the NPY/AgRP neurons in all likelihood signals via the VTA to promote consumption of energy dense foods, an effect dependant on opioid signalling. Circulating ghrelin also reaches the VTA directly, and can increase both feeding and motivated responding, although the downstream pathways are divergent. Taken together, the hypothalamic and mesolimbic pathways represent a convergent evolution of ghrelin function, which promotes positive energy balance through both increased food intake and increased motivational drive to obtain food.

3. INSULIN AND LEPTIN

High circulating ghrelin levels are accompanied by low insulin and leptin levels in situations of energy deficit. Low levels of these hormones likely serve to promote activation of various reward and motivational processes, which is similar to the processes described above for ghrelin, signalling through both hypothalamic and VTA pathways. Both the leptin and insulin receptors are expressed on dopaminergic neurons within the VTA [52,53] and ICV administration of either leptin or insulin suppresses responding for a sucrose reinforcer in satiated chow-fed rats [54]. The concept that the relative fluctuating levels of insulin and leptin influence the incentive salience of a food reinforcer is neatly demonstrated by the way rats respond to insulin or leptin treatment in the conditioned place preference (CPP) test. For example, animals treated with ICV insulin or leptin on the test day of a CPP test show reduced preference for the side paired with an energy dense food reinforcer compared to vehicle treated rats, regardless of whether they were...
Review

Review

treated with leptin or insulin during the conditioning phase. However, rats treated with leptin or insulin during conditioning, but not treated on the test day, show the same preference as vehicle treated rats for the side paired with the food reinforcer [55]. This demonstrates that high levels of brain leptin or insulin do not block the ability of the rats to learn about the caloric content and possibly hedonic impact of the food, however high levels of brain insulin and leptin during testing reduce the value or how salient calorie content is to the animal, which manifests as reduced preference for the paired chamber.

Both NPY/AgRP and proopiomelanocortin (POMC) neurons in the hypothalamus are direct targets of leptin and insulin. At normal circulating leptin levels, leptin receptors on the AgRP neurons provide tonic inhibition on these neurons [23]. Removal of this inhibition when leptin levels fall, results in increased excitability of these neurons, which acts in addition to ghrelin’s excitatory action at these cells. Furthermore, studies by Perello et al. show GHSR1α deficiency does not influence leptin’s effects on appetite and body weight [56], however central leptin infusion prevents Fos activation in the arcuate nucleus of the hypothalamus (ARC) in response to GHSR1α agonism [57]. These results suggest hierarchical neuroendocrine control over NPY/AgRP neurons, as removal of leptin tonic inhibition is required to fully maximise ghrelin-induced activation of NPY/AgRP neurons.

The main hypothalamic neuronal type responsible for leptin’s anorexigenic effects is presynaptic GABA-ergic cells that maintain inhibitory control over the POMC cells [58]. These cells do not contain AgRP, although NPY/AgRP cells are also GABA-ergic and have inhibitory inputs onto POMC neurons [59], with cell bodies in the ARC, the DMH, and/or the lateral hypothalamus (LH) [58]. When leptin is present, i.e., in fed conditions, leptin action on these GABA-ergic cells results in disinhibition of POMC neurons. When leptin signalling is removed from these GABA-ergic neurons, the downstream POMC cells become hyperpolarized and cease providing opposition to NPY/AgRP signalling, resulting in increased feeding and obesity [58]. In this way, leptin may also influence signalling through AgRP-mediated motivational effects.

The LH has been described as a key linking nucleus for hypothalamic, mesolimbic and cortical structures [60]. Electrical stimulation of the LH is pleasurable and conditions an operant response, possibly due to the extensive innervation of the VTA dopaminergic neurons. Using pSTAT3 as a marker of leptin activated cells, both the NPY/AgRP and POMC neurons show increased pSTAT3, indicating direct leptin modulation of these neurons via autoreceptors [80,81] as well as likely inhibiting NPY/AgRP neuronal activity [82]. In both the POMC and NPY/AgRP populations, it is in a key position to integrate cortical information about higher order behavioural outcomes with base metabolic information conveyed via hypothalamic circuits.

Both the insulin and leptin receptors heavily co-localise with tyrosine hydroxylase staining in the VTA [52,66] and exogenous administration of leptin and insulin into the brain can directly modulate dopaminergic signalling [67]. Fasting decreases DAT activity, which can be reversed in vitro in cell preparations by incubation with insulin [13]. Further to this, intra-VTA insulin injections increase activity of the dopamine transporter (DAT) and reduce dopamine availability in the VTA [68]. While this study did not examine the effects of VTA insulin in forebrain structures more likely to directly mediate motivated behaviour, others have shown that ablating insulin production with streptozotocin (STZ) decreases DAT activity, and thus increases dopamine availability in the striatum [69]. This appears to have functional consequences as STZ-treated rats show increased susceptibility to forming a conditioned place preference to morphine [70], similar to effects seen in DAT knockout mice, which also display constitutively high dopamine levels.

Leptin directly modulates the responsiveness of midbrain dopaminergic neurons. Using pSTAT3 as a marker of leptin activated cells, both the dopaminergic and GABA-ergic population have been shown to be leptin responsive, with a relatively greater proportion of TH positive cells showing pSTAT3 staining [66,71]. At least some of these pSTAT3 positive cells project to the NAc [71], and leptin administration reduces both firing rate of dopamine neurons [66] and dopamine efflux in the NAc [72]. Knockdown of the leptin receptor within the VTA by siRNA increases responding for a sucrose reinforcer on a progressive ratio task [73]. Interestingly, knockdown of this leptin receptor population does not affect fixed ratio responding [73] or sucrose preference in a free choice two bottle paradigm [74], consistent with the idea that reduced leptin signalling in the VTA primarily influences motivational drive rather than hedonic consumption. These receptors also mediate anxiety-related behaviour [74] through signalling to the amygdala, another target structure of the VTA dopaminergic neurons.

In rats, refeeding following a fast is associated with a NAc dopamine spike, which is suppressed when rats are given leptin before refeeding [72]. Intact dopamine signalling is critical for the motivation to eat [75], even in the absence of leptin, a situation that usually drives extreme hyperphagia [76]. Conversely, viral knockdown of the leptin receptor in the VTA of mice results in increased feeding and locomotor activity [66]. These findings suggest that the ability of leptin to suppress feeding is predicated on an intact dopaminergic system as the ultimate effector mechanism to drive consumption.

4. OPIOID SIGNALLING IN MOTIVATION AND HEDONICS

The VTA and associated neural circuits are generally considered the backbone of the reward pathway. The VTA receives input from LH [60], as well as from the nucleus of the solitary tract (NTS) in the brainstem [77], an area which integrates afferent signals from the viscera. As mentioned above, it is directly sensitive to leptin and insulin levels and VTA neurons are sensitive to glucose [78]. Closely associated with VTA neurocircuitry are the opioid receptors. Opioid receptors, particularly the MOR, are often associated with hedonic processing, but the opioid receptors are widely expressed throughout the brain and have broad involvement in many processes including homeostatically driven feeding behaviour. Alternative post-translational processing of POMC yields beta endorphin, an agonist for the inhibitory G protein coupled MOR [79]. Beta endorphin released from POMC cells inhibits POMC neurons via autoreceptors [80,81] as well as likely inhibiting NPY/AgRP neuronal activity [82]. In both the POMC and NPY/AgRP populations, it has been speculated that beta endorphin serves to shut down persistent neural activity, so opioid signalling within the hypothalamus may form part of a local regulatory circuit.

Opioid receptor expression within the VTA regulates dopaminergic tone and can modulate motivational processes. Injection of MOR agonists into the VTA increases dopamine release in the NAc [83], and increases feeding in fasted rats and satiated rats [84,85]. Recent work has shown that opioid and dopamine signalling in the NAc can amplify incentive salience of cues [86], so it may be that metabolic signals act to increase
baseline drive, and opioid and dopaminergic signalling in the NAc further promotes motivated behaviour. The possibility that amplification of an incentive salience signal by the NAc may push cue-dependent motivated behaviour may have implications for failure of diets designed to induce weight loss, as fMRI imaging shows hungry human subjects also have enhanced appetitive cue-responses [87]. In this situation, dopaminergic amplification of the incentive salience of food cues in the NAc may make those cues impossible to resist, leading to ‘cheating’ on the diet. The hedonic aspects of the eating experience seem to stem from the NAc which generates the hedonic response to metabolically relevant taste stimuli, such as sweet and fatty [88]. The involvement of opioid receptors in the ventral striatum in such processes has been known for some time [89], but recent work has localised this phenomena to a small area in the medial shell of the NAc, which has been named the ‘hedonic hotspot’ [90]. Opioid signalling in this ‘hotspot’ mediates feeding behaviour, with opioid agonists increasing the ‘liking’ of a sweet taste and inducing feeding [90]. A similar area exists within the interconnected ventral pallidum [91]. These responses seem particularly to rely upon signalling by the MOR, although cannabinoid receptor 1 activation in this area is also able to produce increased hedonic reactions to taste [92]. There is a little doubt that opioid activation in areas of the NAc shell is associated with heightened enjoyment of food and eating [93], however whether metabolic signals modulate this response is unclear. As pointed out recently, ‘the difference between dopamine and mu opioid effects in the NAc is not that opioids always cause increased ‘liking’ but not ‘wanting’, whereas dopamine causes ‘wanting’ but not ‘liking’’ [86], rather the relationship is much more complex. Currently, there is a lack of empirical evidence to support the idea of metabolic modulation of pure hedonic reaction to taste, however it will be interesting to see if such modulation can be demonstrated. There is some evidence that fasting enhances the ability to detect sweet or salty taste in solution in humans, with different methodologies confirming [94] or debunking the idea [95]. Diurnal leptin levels have been linked to the ability to detect sweet taste, with greater sensitivity achieved when leptin levels are low [96]. Similar reports have been made regarding olfactory acuity in rats, where fasted rats show greater ability than satiated rats to detect both neutral and aversive odours [97,98]. Administration of insulin blunts this effect, rendering fasted rats no better at odour detection than satiated ones and abolishing sniffing in response to food odour [98]. High ghrelin levels similarly have a sensitising effect and enhance sniffing behaviour in both rodents and humans, but do not alter pleasantness as rated by human subjects [99]. Critically, in both rodents and humans the sensitisation occurs regardless of hedonic impact of the scent, demonstrating a general heightened processing is misleading, and careful consideration and reporting of the exact mesolimbic processes being manipulated will greatly benefit the field of metabolic science.

5. CONCLUSION

Energy deficit serves to alter motivational state by increasing the incentive salience of certain reinforcers. This fact has been exploited widely in behavioural research to encourage animals to perform or learn a task they are otherwise disinclined to do. How the brain senses internal energy status and transduces that signal into increased motivation is not clear. We postulate that the hormonal signature of hunger (i.e. high ghrelin and low leptin and insulin levels) serves as a metabolic signature that promotes increased dopaminergic signalling, most prominently through modulation of dopamine uptake. This ultimately manifests as increased motivation to work for a reinforcer, and serves to alter the incentive salience of food in line with metabolic need. Motivation and reinforcer value are the mesolimbic processes most affected by metabolic needs. There is little evidence that hunger, or the hormonal signature of hunger, increases in hedonic impact of food through heightened enjoyment of taste. It is possible that this hormonal signature works to a more than additive, possibly synergistic, amplification of motivation particularly through the opposing actions of the hormones leptin and ghrelin in a number of neural circuits. The example of NPY/AgRP neurons, which are activated by high ghrelin levels and disinhibited by low leptin levels, demonstrates that these signals can act in a co-ordinated way to produce increased drive to eat. Additionally, there are other hormonal signals such as GLP-1 and amylin which are known to act in reward pathways and may provide further levels of augmentation of the motivational response to energy deficit. Both of these hormones are satiety signals and can signal through the VTA to reduce feeding [77,100], and also modulate motivated responding [100,101]. In addition, there may be direct actions of altered humoral fatty acid and/or glucose levels on neuronal populations responsible for parsing motivation. The way in which these signals interact with the hormones discussed here remains to be examined. As outlined in Section 1, using the catch-all term of ‘reward’ to describe all mesolimbic processes has led to confusion in the literature. Others have made a concerted effort to disambiguate the term and to provide a lexicon to describe the complex behaviours encapsulated within the broader concept of ‘reward’ [2,3]. In summary, we believe that a metabolic signature of energy deficit, such as high ghrelin and low leptin and insulin, increases the incentive salience or the value of a food reinforcer. The idea that metabolic need alters ‘reward’ processing is misleading, and careful consideration and reporting of the exact mesolimbic processes being manipulated will greatly benefit the field of metabolic science.

CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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