Role of orexin and opioid dynorphin peptides in obesity behavioral dysregulation

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Orexin, feeding and foraging

Food-seeking behavior and uncertainty

Uncertainty can be understood as a measure of the expectation of the reward prediction error in a given environment. This measure of the difference between expected reward and current reward is encoded by dopamine neurons (Bayer and Glimcher 2005). Furthermore, this system can modify decision-making policies based on the reward-prediction error (Pessiglione et al. 2006). Food-seeking behavior can be conceptualized as series of decision-making actions occurring in an environment with varying grades of uncertainty, where the reward prediction error evaluates each feeding bout, and over a history of bouts, uncertainty over environment rewards is obtained.

Under higher uncertainty levels of environment food disposition, animal food-seeking bouts are increased, resulting in hoarding-type behavior, arguably a mechanism to prevent possible starvation (Anselme and Güntürkün 2019). However, this behavior can also be explained by food scarcity or insufficient energetic supply by the environment. The latter case does not necessarily predict uncertainty as this can be high on average, but volatile from time to time. Nevertheless, when constant food position changes alter feeding environment, an increased intake is observed (Forkman 1993), so food access variability can trigger, by itself, an increased food-seeking behavior. Sign-tracking also increases when uncertainty about reward probabilities also increases (Anselme, Robinson, and Berridge 2013). That is, motivation is increased under the uncertainty of reward delivery. In addition to modifying intake, uncertainty levels can affect energy expenditure (Bednekoff and Houston 1994), even when overall food levels are equated in predictable and unpredictable setting (Cuthill 2000).

If uncertainty can modulate food-seeking behavior in order to increase intake and better sustain energetic reserves. It is expected to have at least, to functional instances (1) a uncertainty sensing unit and (2) a reward processing unit, which can relay information to homeostatic-related and decision-making loci, to integrate such information a determine the next action to take. In humans such functional instances seems to be separated, where nucleus accumbens, thalamus and medial orbitofrontal cortex are more activated in unpredictable reward scenarios, and predictable scenarios with right superior temporal gyrus (Tanaka et al. 2006). Task-related brain activity is reduced in more predictable environments, likely by lowering mean prediction error, however, anterior cingulate cortex (ACC), shows augmented activation when predictability drops (Davis, Choi, and Benoit 2010). When situated in a learning task, ventral striatum has been related to short-term reward prediction, whereas dorsal striatum was related with long-term reward prediction (Tanaka et al. 2006). Short-term reward prediction is closely related to uncertain environments as immediate rewards don't provide any information about subsequent rewards, which is the opposite case of certain (or regular) environments, where each rewards provide all information to predict the next reward. Direct tracking of environment volatility shows that this is well represented in ACC, moreover, this ACC activity is modulated by volatility when reward is observed after an action is made, so the observed effect might imply a modulation of value assigned to the outcome given environment uncertainty (Behrens et al. 2007).

Although the factor determining obesity as an outcome are multiple (Ang et al. 2013), it is reasonable to assume that the more immediate cause is excess intake relative to energetic demands. Moreover, excess of intake is determined in a instance to instance basis, where a decision considering short and long-term benefits/risk must be made. With this in consideration, one can assume that obesity, in part, is caused by sub-optimal short/long-term benefit/risk assessments when taking feeding decisions. If this was the case, as previously noted, areas that are related to compute options value in the short/long term, such as de ACC should be in someway impaired. Delay discouting referers to the depreciation of a certain reward as function of the time required to obtain it (da Matta, Gonçalves, and Bizarro 2012), as such is provides a measures of how reward-related systems bias decision to short or long term. Obese subjects show a robust tendency to steeply discount future rewards (Amlung et al. 2016), thus, favoring short-term rewards.

Furthermore, ACC, among other structures, shows relative atrophy in obese subjects (Wang et al. 2017; Raji et al. 2009), suggesting an impairment of the previously mentioned functions. This findings can be interpreted as if an impairment in environment uncertainty assessment results in a preference for short-term rewards. If this were the case, palatable food sensory cues, which trigger food-intake, would dominate over more, long-term modulated, decisions, such as healthy food intake (Higgs 2016).

Up to this point, the way reward-related systems interact with environment uncertainty has been discussed. Several structures seem to be involved in integrating reward value in face of environment volatility. Moreover, empirical findings of food-seeking behavior in predictable/unpredictable environments were pointed, however, the direct mechanism that guides food-seeking behavior is lacking. One such system is the Orexin/Hypocretin (HO), which is part of energy homeostatic and feeding pathways (Toshinai et al. 2003), and plays a large role in increasing food intake (Wolf 2009). However, a more broad and complex opioid system is thought to control food intake, which in turn is modulated by food preference and selective to certain macro-nutrients, such as fat (Taha 2010). More recent evidence has linked the activation of hypothalamic HO system to an increase in short-term spatial memory, which is function that supports exploratory foraging behavior (Aitta-aho et al. 2016).

Moreover, orexin promotion of such foraging-related behavior has been postulated as one of its main functions (Barson 2020). Such function is relevant because foraging behavior evolved in a specific type of environment, where resources are sparse, clustered and in potential risk of predation, and developed relatively stable strategies to deal with such conditions (Wosniack et al. 2017). Thus, foraging behavior, seeks to generate a strategy to maximize energetic intake in a partially known environment, however, if environment resource are non-depleting it can lead to behaviors such as binge eating, finally resulting in excess caloric intake (Barson 2020).

To provide a connection between food-seeking behavior and uncertainty, evidence on the effects of increasing such uncertainty on the proximal effect of food-seeking behavior, that is, food intake, is neccessary. In that regard, it was pointed that, possibly because of survival mechanisms, environment uncertainty increased food intake and reduced energetic spending. Then, the sufficient functions to support such findings were discussed, emphasizing related structures and functions associated with each on to be accounted by problems with delayed-discounting and ACC atrophy, which points towards a sub-optimal pairing between reward value assignment given environment uncertainty levels. Also, OH system role in foraging was discussed as a proximal cause of overfeeding. Together, this suggests that food-seeking behavior evolved to provide optimal decision-making strategies in uncertain and scarce environments, however, (1) when environment energetic density is high, such strategies would result in overfeeding and (2) obesity in itself can impair homeostatic regulation by altering structures related to uncertainty and reward value processing. Previous points, predict that underlying foraging mechanisms, in certain environments, can lead to obesity. to be accounted by problems with delayed-discounting and ACC atrophy, which points towards a sub-optimal pairing between reward value assignment given environment uncertainty levels. Also, OH system role in foraging was discussed as a proximal cause of overfeeding. Together, this suggests that food-seeking behavior evolved to provide optimal decision-making strategies in uncertain and scarce environments, however, (1) when environment energetic density is high, such strategies would result in overfeeding and (2) obesity in itself can impair homeostatic regulation by altering structures related to uncertainty and reward value processing. Previous points, predict that underlying foraging mechanisms, in certain environments, can lead to obesity.

Obesogenic environments

Cafeteria diet and uncertainty

The decision making problem in obesity

Conclusions

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