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Commentary

Behavioral Consequences of a Rumbling Tummy: Fasting Alters Emotional State via the Vagus Nerve

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For animals, survival is greatly enhanced by the ability to adapt to facilitate the meeting of physiological needs in an ever-changing world. These adaptations can be physiological, such as the shedding a heavy coat of fur in warm weather, or behavioral, such as snuggling up to another animal in cold weather. Such behavioral changes, brought about by sensory information from the environment, are facilitated by psychological shifts in motivation, attention, and emotional responses. In the current issue of *Biological Psychiatry*, Krieger *et al.* (1) investigate mechanisms driving reductions in anxiety-like behavior that occur during fasting. Using 4 different measures of anxiety-like behavior, Krieger *et al.* (1) show that both male and female rodents who are hungry (fasted overnight) display reductions in anxiety-like behavior, measured as an increased exploration of adverse environments, an increased willingness to try unfamiliar foods, and a reduced startle response to loud noises. Research has shown that both acute and chronic food restriction reduce anxiety-like behavior in male rodents (2). Moreover, a recent meta-analysis of 11 studies and 1436 participants showed that fasting alleviated stress, anxiety, and depressive symptoms in humans (3). A question remains as to why such a phenomenon would occur, biologically. What is the potential advantage of having an anxiolytic response to fasting?

When anxious, attention is focused toward threat-related information (attentional bias) and away from task-relevant information (4). When hungry, finding food is an essential task that requires exploration and a willingness to take risks, such as trying new potential food sources. However, when food is not an imminent issue, other aspects that are critical for survival may take precedence, such as remaining hidden from predators and avoiding other potential dangers, such as poisonous foods. A psychological shift in emotional state, whereby fear of predators and unfamiliar foods is lessened, for example, may facilitate the type of behavior likely to result in food foraging success. Whether this adaptation is in fact a biological advantage or not, the question remains: what causes the psychological shift? How do emotional regulatory centers in the brain "sense" changes in energy state?

Kreiger *et al.* (1) next sought to determine the biological mechanism by which emotional states are shifted in accordance with prandial status. They focused on the vagus nerve, which receives meal-related sensory information from the gut, as a potential pathway by which neural activity is altered by meal-related cues to facilitate an anxiolytic emotional state. While similar studies have previously investigated a similar hypothesis with supporting results, Krieger *et al.* (1) provide new insights into mechanisms by which hunger impacts anxiety-like behavior via the vagus nerve (Figure 1). Klarer *et al.* (5) previously used a subdiaphragmatic vagal deafferentation procedure, which eliminates 100% of vagal afferent signaling and 50% of motor efferent vagal communication, to show that vagal communication modulates innate anxiety and learned fear responses. Krieger *et al.* (1) built on this work, using a dual virus chemogenetic approach to temporarily either activate or silence vagal afferent communication from the stomach and duodenum. Chemogenetic activation of sensory vagal afferents reduced anxiety-like behavior across 3 experimental tests, each of which is of high relevance for the type of behavior necessary to secure food: the open field, elevated plus maze (both of which assessed as reduced distance traveled in the open areas), and food neophobia tasks. However, silencing gut to brain vagal communication during refeeding after a fast caused an anxiolytic response in both male and female rats across all 4 behavioral tasks.

An unavoidable problem with rodent behavioral work is related to interpretation; how can we be certain the intended measure (i.e., anxiety) is indeed what is being measured when it is not possible to know the animal's emotional state? In some of the first reports of the use of the elevated plus maze strategy for measuring rodent behavior, Montgomery (6) postulated that exploratory behavior in rodents into open versus closed arms could be driven either by a reduction in fear/anxiety or by an increased motivation to explore independent of fear/anxiety. These two states are likely not exclusive, and it could be argued that the expression of exploratory behavior necessitates a temporary "forgetting" or reduced attention to fears/anxiety. Changes in locomotor activity could also be responsible for behavioral results independent of anxiety responses. For this reason, Krieger *et al.* (1) analyzed their behavioral data adjusting for locomotor activity. However, anxiety may influence locomotor activity via increases in cortical excitability and muscle activity (action readiness), as well as promote the initiation of movement to implement threat related behavioral responses (4). Thus, it is not entirely certain whether there is a need to adjust for locomotor activity, as it may be a component of anxiety-like behavior. Krieger *et al.* (1) commendably address this issue and incorporate a movement-independent measure of anxiety-like behavior, the acoustic startle task, which has no apparent direct confounds resulting from locomotor activity. On one hand, in the acoustic startle task, in which a rodent is exposed to a loud noise and the amplitude of how high the animal jumps

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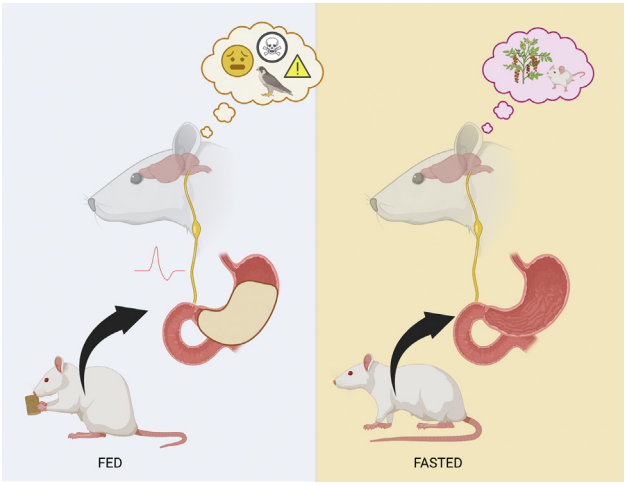

Figure 1. Gut-derived signaling modulates emotional responses to fasting via the vagus nerve. Krieger *et al.* (1) identify a pathway from the gut to the central nucleus of the amygdala that mediates reductions in anxiety-like behavior during fasting. An anxiolytic shift in emotional state, whereby fear of predators and unfamiliar foods is lessened, may facilitate exploratory behavior and facilitate the discovery of a food supply by reducing the fear of new or unfamiliar foods.

when startled is measured, chemogenetic activation of gut-derived vagal afferents had no effect on anxiety-like behavior; on the other hand, chemogenetic inhibition of gut-derived vagal afferents reduced the startle amplitude in rats following refeeding after a fast (1). These findings suggest that activation of vagal afferents by the presence of food in the stomach and/or duodenum is necessary to attenuate the anxiolytic state induced by fasting. However, activation of these gut-derived vagal afferents per se does not promote the startle response. Perhaps an additional food- or gut-derived signal is necessary to fully induce a biological shift in behavioral anxiety-like responses to upper gastrointestinal tract vagal afferent nerve stimulation.

To further interrogate whether gut-derived vagal afferent signaling mediates fasting-induced "tuning" of anxiety-like behavioral responses, Krieger *et al.* (1) used an exciting and novel cholecystokinin saporin (CCK-SAP) method to selectively ablate CCK receptor–containing vagal afferent neurons that innervate the stomach and upper gastrointestinal tract while keeping the efferent communication and lower intestine vagal afferents completely intact (7). Surprisingly, results differed largely from chemogenetic experimental findings, in that there was a sex-specific effect of CCK-SAP to increase locomotor activity and startle amplitude, which occurred in males only. These findings could be due to acute versus chronic deactivation of vagal afferent signaling, or perhaps to the more discriminative ablation of the CCK receptor–containing cell type. In addition, CCK-SAP animals were not explicitly tested in the fasted or refed states, whereas chemogenetic inhibition was tested during fasting and after 1 hour of refeeding, which is indicative of more of an acute impact and may be an important distinction for the interpretation of these findings.

Using polysynaptic tracing to identify cells synaptically downstream from vagal afferent neurons, Krieger *et al.* (1) observed extensive labeling in the central nucleus of the amygdala (CeA) with minimal labeling in the bed nucleus of the stria terminalis. The CeA and the bed nucleus of the stria terminalis are a part of the extended amygdala, and together these regions play a role both in mediating anxiety-like behavior and in the expression of conditioned fear responses (8). Early reports suggested that the CeA mediates conditioned fear responses, and the bed nucleus of the stria terminalis is more implicated in general anxiety to a nonspecific stimulus; however, this theory was largely based on findings that AMPA receptor antagonists had no effect on light-enhanced startle responses (8). Krieger *et al.* (1) show that CCK-SAP–mediated selective ablation of vagal afferent signaling reduces anxiety-like behavior by engaging GABAergic (gamma-aminobutyric acidergic) signaling in the CeA. While CCK-SAP selective deafferentation reduced the startle response compared with control injected animals, the $GABA_A$ receptor antagonist bicuculline in the CeA attenuated the reduced startle responses resulting from deafferentation. These findings suggest that the CeA does mediate nonconditioned fear-based anxiety-like responses associated with certain internal contexts.

Krieger *et al.* (1) raise an interesting question regarding the relationship between diet and anxiety disorders. Anxiety disorders are characterized by extreme fear of and hypervigilance to perceived threats, but fear and hypervigilance are also important responses to environmental safety that can prevent catastrophic and often fatal outcomes.

This study suggests that gut sensory vagal signaling modulates anxiety-like behavioral responses to fasting—is it also the case that chronic overnutrition or specific dietary factors facilitate alterations in sensory-afferent signaling pathways that facilitate susceptibility to anxiety disorders? Evidence from human studies points to an association between dietary patterns and anxiety disorders, and in rodent studies, consumption of a Western diet, high in saturated fat and added sugars, particularly during early-life developmental periods, has been shown to increase anxiety-like behavior later in life (9). Future research investigating the link between diet and anxiety disorders may want to consider investigating vagal communication as a mechanistic link by which diet alters our "gut feelings."

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Article Information

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