Brain, Behavior, and Immunity 78 (2019) 7–8

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Brief Commentary

Anxiety in obesity: Is neuroinflammation the critical link?

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Obesity is a major global public health concern with nearly one-third of the world population categorized as overweight or obese. Obesity is associated with increased morbidity and mortality and has enduring effects on individual's physical, social, and even emotional health. Indeed, the prevalence of neuropsychiatric conditions, including depression and anxiety increases with obesity (Baker et al., 2017); however, mechanisms mediating the bi-directional relationship between obesity and changes in mental health are not fully understood. In this issue of *Brain, Behavior, and Immunity*, Fourrier et al. (2019) provide novel evidence that hippocampal tumor necrosis factor-α (TNF-α) mediates obesity-related anxiety-like behaviors in mice (Fourrier et al., 2019).

One hallmark of obesity is chronic inflammation, which may contribute to behavioral issues associated with obesity. The first revelation of inflammatory dysregulation in obesity was elevated expression of the pro-inflammatory cytokine TNF-α in adipose tissue of obese mice (Hotamisligil et al., 1993). Subsequent work demonstrated enlarged adipocytes that occur with obesity recruit macrophages and can promote the release of pro-inflammatory cytokines, which elicit systemic low-grade inflammation (Weisberg et al., 2003). Obesity-related inflammation is not just limited to the periphery; hypothalamic inflammation develops rapidly following consumption of a high-fat diet and persists following weight gain (Thaler et al., 2012). Hypothalamic inflammation is considered both a consequence of and risk factor for obesity, as inflammation in the hypothalamus can dysregulate integration of metabolic feedback signals leading to weight gain (Thaler et al., 2012). Furthermore, exaggerated immune responses contribute to neuropsychiatric comorbidities associated with obesity, including anxiety and depression (Baker et al., 2017; Dantzer et al., 2008). Anti-inflammatory treatments can improve depressive symptoms in patients with baseline elevations in inflammatory cytokines (Raison et al., 2013). Similarly, decreased levels of inflammatory cytokines caused by weight loss in obese individuals correlate with reduced anxiety (Capuron et al., 2011). Therefore, understanding the mechanisms that link obesity-associated neuroinflammation and anxiety could aid development of novel anxiolytic drug therapies that target inflammatory pathways.

In this issue of *Brain, Behavior, and Immunity*, Fourrier et al. (2019) hypothesized that obesity-induced increases in inflammatory cytokines in brain lead to increased anxiety-like behaviors in mice (Fourrier et al., 2019). Obesity was studied in male mice using the well-established *db/db* leptin receptor-deficient model. *db/+* control and *db/db* mice underwent several treatments targeting inflammatory pathways: chronic food restriction (CFR), oral ibuprofen, and intracerebroventricular administration of the TNF-α blocker etanercept. The study established that obese male mice exhibit elevated anxiety-like behaviors concomitant with increased expression of pro-inflammatory cytokines in several brain regions involved in emotional regulation, such as the hippocampus and prefrontal cortex**.** Anti-inflammatory treatments, including CFR and oral ibuprofen, ameliorated anxiety-like behaviors in *db/db* mice. Furthermore, ibuprofen and CFR treatments blocked elevated hippocampal TNF-α expression in db/db mice but did not significantly modulate other pro-inflammatory cytokines. This suggests that increased TNF-α in the brain, particularly in the hippocampus, may play a causal role in increases in anxiety-like behaviors in obese mice.

The role of TNF-α in modulating anxiety was subsequently determined by chronically infusing the TNF-α blocker etanercept into the brain and measuring the impact on anxiety-like behaviors and synaptic transmission in the ventral hippocampus. Etanercept selectively reduced anxiety-like behaviors in obese *db/db* mice but not in *db/+* controls in an elevated plus maze test, suggesting increases in anxiety-related behaviors in *db/db* mice are dependent on TNF-α signaling. Changes in synaptic transmission in the hippocampus may underlie anxiety behaviors in obese mice: TNF-α inhibition diminished the frequency and amplitude of excitatory postsynaptic currents in the ventral hippocampus, a region of the brain associated with mood regulation. Etanercept injections are currently used clinically to treat conditions of chronic inflammation, including rheumatoid arthritis and psoriasis. Accordingly, this TNF-α blocker could be a promising therapeutic candidate for treating anxiety in obese individuals.

Results presented by Fourrier et al. (2019) lead to several avenues for future work. First, obesity rates are higher in adult women across diverse ethnic backgrounds (Hales et al., 2017) and women are almost twice as likely to suffer from anxiety than men (Donner and Lowry, 2013). Determining whether changes in neuroimmune activation may lead to the anxiety bias in females in the context of obesity and/or other

DOI of original article: https://doi.org/10.1016/j.bbi.2018.11.316

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https://doi.org/10.1016/j.bbi.2019.01.008
Received 10 January 2019; Received in revised form 11 January 2019; Accepted 12 January 2019
Available online 15 January 2019

conditions that activate the immune system is critical. Second, this study was performed in adolescent (five-week-old) mice. The prevalence of obesity in humans is greatest for middle-aged adults. For example, in the United States the prevalence among middle-aged adults is 42.8% compared to nearly half that, 20.6%, during adolescence (Hales et al., 2017). Given that age modulates neuroinflammatory responses, future work should establish the efficacy of a TNF-α blocker like etanercept in reducing anxiety-like behaviors in adult and aged mice. Finally, determining the mechanisms by which TNF-α targets synaptic transmission and the cellular players involved could provide critical information for developing novel targets for treating anxiety disorders.

Unique biological underpinnings may cause mood disorders that have traditionally been treated with a one-size-fits-all approach. This lack of consideration of the potentially distinct mechanisms underlying these conditions has likely contributed to the high rate of treatment resistance. Growing evidence implicates changes in immune pathways in contributing to anxiety (Baker et al., 2017) and depressive disorders (Raison et al., 2013) in a subset of cases. The conclusions presented by Fourrier et al (2019) provide novel evidence supporting a role for TNF-α in obesity-associated anxiety. This mechanistic link may prove key to future therapies targeting anxiety disorders, in the context of obesity as well as other conditions that lead to neuroimmune activation.

1. Refers to

Célia Fourrier, Clémentine Bosch-Boujua, Raphaël Boursereau, Julie Sauvant, Agnès Aubert, Lucile Capuron, Guillaume Ferreira, Sophie Layé, Nathalie Castanon

Brain tumor necrosis factor-α mediates anxiety-like behavior in a mouse model of severe obesity

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