Fibroblast Growth Factor-2: A Promising Biomarker for Anxiety and Trauma Disorders

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Journal of Experimental Neuroscience
Volume 11: 1–3

DOI: 10.1177/1179069517749589

ABSTRACT: Anxiety and trauma disorders are a significant source of global burden. Although it is clear that there is great heterogeneity in humans' response to trauma and stress, most research on fear and anxiety has focused on the "average" animal. Increased understanding of the sources of individual differences in fear reactions may lead to more refined means of predicting who is at risk for the development of anxiety disorders so that early preventative interventions can be implemented. This commentary highlights recent cross-species work (in rats and humans) indicating that the neurotrophin fibroblast growth factor-2 (FGF2) holds promise as a potential biomarker for anxiety disorder vulnerability. Both central (hippocampal) and peripheral (serum and saliva) markers of FGF2 correlate negatively with fear expression after an aversive conditioning experience. Here, 2 broad accounts of the potential mechanism of vulnerability captured by measures of FGF2 are outlined. In particular, it is suggested that basal differences in FGF2 (across different tissue types) may provide a general index of one's regenerative capacity; alternatively, differences in FGF2 reactivity (in specific tissue types) may be indicative of one's coping capacity in response to stress.

KEYWORDS: Fibroblast growth factor-2, anxiety disorders, trauma, salivary biomarker, individual differences

RECEIVED: November 28, 2017. **ACCEPTED:** November 30, 2017.

TYPE: Invited Commentary

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Comment on:

Graham BM, Zagic D, Richardson R. Low endogenous fibroblast growth factor 2 levels are associated with heightened conditioned fear expression in rats and humans. *Biol Psychiatry*. 2017;82:601-607.

Anxiety and trauma disorders are the most common classes of mental illness, affecting 1 in 9 people in any given year globally.[1] In terms of disability-adjusted life years, a standard index of global burden, anxiety disorders are the sixth leading cause of disability.[2] Although recent estimates of economic burden are lacking, the annual financial cost of anxiety disorders in the 1990s was estimated to be US $42 billion.[3] To reduce this burden, there is a clear need to develop means of identifying individuals at risk of anxiety so that early preventative measures can be put in place. Critically, in this regard, although stress or trauma exposure often contributes directly or indirectly to the development of anxiety disorders, there are large individual differences in humans' fear responses and their capacity to regulate fear. As just one example, around half to two-thirds of people across the world experience significant trauma, yet lifetime prevalence rates of posttraumatic stress disorder range between 2% and 20%, suggesting that most people are highly resilient even when faced with extreme adversity.[4] Identifying the factors that predict variability in fear responses is critical to understand why some people are resilient, and others more vulnerable, to the development of anxiety.

Key features of anxiety disorders can be modeled in the laboratory in human and nonhuman animals using a variety of procedures. Fear expression can be induced by mere exposure to innately fearful stimuli, such as predator odor, bright open spaces, psychosocial stress, and heights (ie, unlearned fear). Fear can also be conditioned by pairing initially neutral stimuli (termed "conditioned stimuli") with aversive stimuli, such that subsequent exposure to the conditioned stimuli provokes species-specific defense responses, such as freezing in rodents and skin conductance responses in humans. Examination of the processes underlying unlearned and conditioned fear in laboratory models can provide critical insights to the neurobiological and psychological mechanisms by which animals cope with fear. Most of this research has focused on how these processes operate in the "average" animal, but there are large individual differences in unlearned and conditioned fear expression, with "subpopulations" that exhibit heightened fear expression.[5] Although rarely studied, such cases echo the heterogeneity of humans' responses to trauma, and exploring the neurobiological factors underlying individual differences in fear expression is likely to identify specific, targetable, potentially tractable variables that foster vulnerability or resilience.

Recent research has suggested that the neurotrophin fibroblast growth factor-2 (FGF2) may be an endogenous regulator of fear expression.[6] FGF2 is a protein involved in a range of physiological actions, such as neuroregeneration and stress regulation.[7] Phenotypic differences in unlearned fear among selectively bred rats are negatively correlated with hippocampal FGF2 gene expression, where FGF2 messenger RNA is greater among rats that exhibit low levels of unlearned fear.[8] Similarly, rats that exhibit low levels of conditioned fear expression have higher hippocampal FGF2 protein levels relative to rats that exhibit high levels of conditioned fear expression,[9] an effect that is apparently stable, being evident even 3 months after

behavioral testing.[10] Increasing FGF2 directly (through FGF2 injections) or indirectly (through environmental enrichment) reduces unlearned and conditioned fear expression in rats,[8,11] whereas unlearned fear is augmented in rats with viral-mediated knockdown of FGF2 function[12] and in mice that lack a functional FGF2 gene.[13] Together, this suggests that FGF2 may be causally involved in individual differences in fear expression and thus may represent a novel biomarker of relative susceptibility to anxiety.

Until recently, all existing research on FGF2 and anxiety had exclusively focused on central (ie, hippocampal) measures of FGF2 in rodents. It was unknown whether a similar relationship between FGF2 and fear existed in humans and, moreover, it was unknown whether peripheral markers of FGF2 (eg, in serum or saliva), that can be easily and noninvasively obtained from humans, correlated with fear in the same way as that established for the hippocampus. In a recent study published in *Biological Psychiatry*, we tested both of these issues.[14] Focusing initially on rats, we demonstrated that at baseline, hippocampal levels of FGF2 protein correlated positively with levels of FGF2 protein expressed in serum. In turn, we showed that serum FGF2 correlated negatively with conditioned fear expression in rats, with a similar strength to that which we previously described for hippocampal FGF2. Finally, in a large sample of healthy humans subjected to a differential fear conditioning procedure (in which participants learn to differentiate between a threatening and a safe stimulus), salivary FGF2 negatively correlated with fear expression toward both stimuli. That is, people with lower FGF2 exhibited greater fear responses to both the threatening and the safe stimulus, suggestive of an overgeneralized fear response, as has been observed in anxious populations previously.[5]

These findings are encouraging because the cross-species generalizability of the relationship between FGF2 and fear expression suggests that continued research on FGF2 in rodents, in which potential downstream mediators of FGF2's effects can be examined with greater precision than what can be achieved in research on humans, may lead to further insights that will likely be applicable to humans. Moreover, they suggest that FGF2 holds promise as a potential biomarker for anxiety and trauma disorders that can be easily measured in humans. If this is the case, then it would be anticipated that individuals with anxiety and trauma disorders should have lower levels of salivary FGF2 compared with nonanxious individuals, a possibility that awaits testing and which raises a number of questions. In particular, what aspect of vulnerability to anxiety might be captured by salivary FGF2? On the one hand, it could be argued that being a mitogen that is principally responsible for regeneration in response to physical stress throughout the nervous system (eg, FGF2 is involved in regenerative neuroplasticity, angiogenesis, and wound repair),[15] individuals with globally higher FGF2 (ie, indexed from any tissue sample) may be more protected against anxiety due to a generally greater regenerative capacity. Such an argument assumes that differences in FGF2 would be evident at baseline (ie, under resting conditions) and relatively stable. This argument is indeed consistent with our report that differences in hippocampal FGF2 were evident 3 months following behavioral testing in rats,[10] and the report that rats selectively bred to show phenotypic differences in unlearned fear exhibits differences in hippocampal FGF2 at baseline.[8] Inconsistent with this argument, on the other hand, is the finding that amygdala and medial prefrontal cortex FGF2 levels show no relationship to fear expression,[9,10] suggesting that, at least centrally, the relationship is selective to specific neural loci. Moreover, in all of our works on FGF2 and learned fear expression (in both rats and humans), FGF2 was assayed after the test for conditioned fear (2 hours or 3 months later in rats and immediately after in humans).[9,10,14] Therefore, it is possible that FGF2 expression was differentially induced by the testing procedures, which are designed to produce fear. Although this possibility is somewhat dubious in the case where the relationship with hippocampal FGF2 was evident 3 months later, we have not tested for a similarly enduring relationship between salivary FGF2 and fear expression in humans.

An alternative argument is that differences in FGF2 expression may be small, or difficult to detect, under basal conditions, but that differences in FGF2 *reactivity* emerge under conditions associated with stress (such as that induced by our testing procedures). This would explain the neural specificity of the effect (eg, it would only be evident in regions responsible for stress regulation, such as the hippocampus). It would also suggest that FGF2 may be secreted into blood circulation as part of the stress response, where it may enter into saliva through passive diffusion, similar to what occurs with cortisol. The salivary glands, which are reservoirs for growth factors including FGF2,[16] may also secrete FGF2 in response to stress. Such peripheral secretion of FGF2 may be part of a more general protective response when exposed to physical or psychological stress. This argument is consistent with reports that acute stress transiently increases hippocampal FGF2 in rats, a response that becomes dysregulated if the stress is uncontrollable[17,18] or following a history of prenatal stress.[19] It is also consistent with a recent report that FGF2 regulates hippocampal glucocorticoid expression.[13] It follows, then, that individuals with reduced FGF2 reactivity in response to stress may have diminished physiological capacity for coping with stress, placing them at increased risk for the development of anxiety. It is also possible that both proposed processes (ie, differences in basal FGF2 that are coupled with differences in FGF2 reactivity) operate simultaneously.

Of course, these suggestions are mainly speculative at this stage. Clearly, much more work is required to understand the functional significance of individual differences in FGF2 with respect to anxiety vulnerability. It is suggested that, to this end, strong inroads should be made by comparing measurements of FGF2 in both nonanxious and clinically anxious populations, under resting conditions and in response to stress. Importantly,

our demonstration that salivary FGF2 is correlated with fear expression in healthy humans provides a proof of concept that further investigations along these lines are likely to be fruitful. Hopefully, such investigations will lead to more refined means of identifying vulnerable individuals, and implementing effective preventative interventions, such that the global prevalence and burden of anxiety can be diminished.

Author Contributions

BMG developed the structure and arguments for the paper, wrote the paper, and approved the final version of the paper.

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