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Fibroblast Growth Factor 2 Sits at the Interface of Stress and Anxiety

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The role of growth factors in the control of mood and emotions has gained considerable interest. In particular, discoveries during the past decade have pointed to the involvement of the fibroblast growth factor (FGF) family in affect regulation and have underscored the ability of one member, FGF2, to decrease depression and anxiety behaviors in animal models (1). In the present report, Salmaso *et al*. (2) show that *Fgf2* knockout (KO) mice exhibit increased anxiety behavior, and this phenotype is rescued by FGF2 administration in adulthood (2). The *Fgf2* KO mice also have decreased glucocorticoid receptor (GR) expression in the hippocampus that is associated with increased hypothalamic-pituitary-adrenal (HPA) axis activity. When the authors blocked GR with RU486, FGF2 was no longer effective on anxiety behavior in the KO mice. The authors suggest that GR is necessary for the anxiety-reducing actions of FGF2. They propose the transcription factor early growth response protein 1 as a potential mediator, because early growth response protein 1 was decreased in *Fgf2* KO mice, rescued by the FGF2 treatment, and associated with the GR promoter in *Fgf2* KO mice. Their interesting findings on the role of FGF2 in this model support and strengthen the literature on the role of this factor in controlling affect. Their conclusions on the role of GR in mediating the effects of FGF2 are novel and interesting, but their conclusions need to be discussed in the context of the complex and often bimodal actions of GR, stress, and anxiety regulation.

Previous work has shown that stable phenotypic differences in anxiety behavior correlate with differences in FGF2 expression and influence the effectiveness of exogenous FGF2 on emotionality. Thus, animals that have been selectively bred to exhibit high levels of anxiety (bLRs) have lower expression of FGF2 in the hippocampus than their less anxious counterparts; indeed, FGF2 expression and anxiety behavior are inversely correlated (1). Chronic administration of FGF2 rescues the anxiety phenotype but only in the high-anxiety animals (Table 1). This reversal is accompanied by increased survival of hippocampal cells selectively in the bLRs that profit from the treatment. Moreover, conditions that increase FGF2, such as environmental enrichment, decreased anxiety behavior only in the highly anxious bLRs (1). Finally, knocking down FGF2 selectively in the hippocampus increased anxiety behavior in outbred rats, demonstrating an ongoing role of FGF2 in the control of spontaneous anxiety (1).

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Remarkably, FGF2 is able to stably and selectively modify the anxiety phenotype during development. When a single injection of FGF2 was administered the day after birth, FGF2 decreased anxiety behavior in the genetically anxious bLRs as adults, without altering the phenotype of the nonanxious animals (3). It would be interesting to determine whether early life FGF2 would also decrease anxiety behavior in the *Fgf2* KO mice and prevent the associated changes in the HPA axis.

In sum, both the previous work and this latest study demonstrate that FGF2 is a particularly effective anxiolytic in highly anxious animals, be it bLR rats or *Fgf2* KO mice. However, it appears less effective under normative or low-anxiety conditions because FGF2 did not alter anxiety-like behavior in *Fgf2* wild-type mice nor in the selectively bred nonanxious rats. This distinction may prove important in considering the interplay between the FGF system and the HPA axis.

A huge body of work has shown that the HPA axis, which is critical for survival, operates in a complex, tightly regulated fashion in terms of both magnitude of change and time domains. Activation of glucocorticoids is critical for survival; however, persistently high levels of glucocorticoids are damaging. Hippocampal GR appears to serve at least two key functions in affect regulation—as a detector of threat that increases anxiety behavior when activated, and as a break for the neuroendocrine stress response by mediating negative feedback that terminates the activation of the HPA axis (4). Which of these functions, threat detection or dampening the stress response, is more evident strongly depends on the specific conditions, including the emotional and neuroendocrine status of the individual.

Studies in several genetic mouse models support the threat detection/anxiety role, because knocking out GR reduces anxiety and overexpressing GR enhances the anxiety phenotype (4). Even without any genetic manipulations, we have shown in the outbred rat that an anxious phenotype is associated with high levels of hippocampal GR (5). Moreover, local hippocampal injections of a GR antagonist reduced spontaneous anxiety selectively in the outbred anxious animals.

By contrast, studies by Meaney's group, as reported in Hellstrom *et al.* (6), have underscored the role of GR as an effective breaking mechanism on the stress response and have shown associated reduction in anxiety behavior. Genetic studies also show that if circulating glucocorticoids are chronically elevated, then enhancing GR activity can activate the breaking mechanism, buffer the stress response, and diminish the negative affect (4). This is clearly the case for the *Fgf2* KO mice—reduced GR levels in dentate granule neurons was accompanied by higher corticotropin-releasing factor in the paraventricular nucleus, which was associated with chronic higher secretion of corticosterone, all consistent with insufficient negative feedback or termination of the stress response. This dysregulated neuroendocrine phenotype was rescued by FGF2 treatment. Because GR blockade prevented this rescue, a sequential model of FGF2 exerting its anxiolytic effects via GR, albeit indirectly, is a reasonable one (2). Interestingly, in this same study GR antagonists reduced anxiety behavior in the *Fgf2* KO model as in the spontaneously anxious rats, further pointing to the complex relationship between GR and anxiety behavior.

Stress is known to affect FGF2 (1). For example, acute stress can increase FGF2 expression, but chronic stress can decrease FGF2 expression. What is less known is how FGF2 alters the HPA axis. Salmaso *et al.* suggest that FGF2 is necessary for maintaining GR expression in the brain and that replenishing FGF2 in adulthood can rescue the decreased GR. There was no significant effect of chronic FGF2 on GR expression in the wild-type animals, underscoring once again the conditional nature of these interactions (Table 1). Given the seminal contributions of Vaccarino and colleagues (7) to our understanding of FGF2 in neural development, it would be beneficial to learn more about the interplay between FGF2 and GR during early development and their combined impact on circuits implicated in emotion regulation.

Under basal states, that is, the absence of a dysregulated HPA axis, we have proposed an opposing relationship between GR and FGF2, with GR serving as a detector of threat and FGF2 serving as an inhibitor of anxiety behavior (8). This is borne out by epigenetic studies showing that relative to low-anxiety animals, highly anxious animals have more binding of the inhibitory histone, H3K9me3 (trimethylation on Lys 9 of histone 3), at the FGF2 promoter and less binding at the GR promoter, consistent with lower FGF2 and higher GR gene expression. This is consistent with GR blockade resulting in decreased anxiety in a variety of models.

However, the relationship seen under basal conditions may alter significantly in cases in which the HPA axis is chronically dysregulated. In those cases, GR blockade may become ineffective because it further exacerbates the increased levels of glucocorticoids that overrides the antithreat signal. Indeed, an early study has shown that blocking GR alone does not ameliorate anxiety under conditions of chronic stress (9). It is likely that in cases such as the *Fgf2* KO model, the most important signal is the persistently high levels of glucocorticoids and ensuing negative affect. Reducing the steroid levels by enhancing GR tone is then permissive for the anxiolytic effects of FGF2. This idea needs to be tested more directly using nongenetic models that lead to chronic HPA disruption.

These ideas are summarized in Table 1 showing that 1) the impact of FGF2 on anxiety behavior is conditional on the animal's affective phenotype; 2) the role of GR on affective behavior is conditional on whether the HPA axis is normal or dysregulated; and 3) the interplay between FGF2 and GR depends on the above conditions, with many variables still needing to be systematically tested.

It is also important to recall that FGF2 is part of a complex family with numerous members and several receptors that interact in complex ways (1). A clear example is FGF9, which acts as an endogenous antagonist to FGF2 (10). The compensatory changes in other members of the family, including the receptors, need to be considered, especially in interpreting genetic studies.

It is clear that the FGF and stress system work coordinately in modulating affective behavior in a context specific, conditional manner. The role of FGF2 seems simpler in that it is consistently anxiolytic but especially effective in anxious phenotypes. The role of GR is more complex in that it functions as a threat detector leading to anxiety but also as a break

that limits high levels of glucocorticoids that themselves are anxiogenic. Unraveling the interplay between these two powerful molecular organizers and modulators of affect may prove extremely valuable in developing novel approaches to the treatment of mood and anxiety disorders.

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Table 1

Complex Interplay Between the Anxiety State of the Animal and the Regulation of the HPA Axis

Interplay	Normally Regulated HPA Axis	Chronically Activated HPA Axis or Chronic Stress
High-Anxiety Phenotype	FGF2 blocks anxiety (1,3)	FGF2 blocks anxiety (2)
	GR antagonist blocks anxiety (5)	GR antagonist prevents anxiolytic effect of FGF2 (2)
	GR: detector of threat	GR: mediator of negative feedback
	Are FGF2 and GR actions sequential or independent mechanisms?	FGF2 actions mediated via GR in genetic model. Is this evident in environmental models of chronic stress?
Normal or Low-Anxiety Phenotype	FGF2 less effective (1)	FGF2 blocks anxiety (Cortney A. Turner, Ph.D., *et al.*, unpublished data, 2016)
	GR antagonist less effective (5)	GR antagonist ineffective (9)
	What is the relationship between FGF2 and GR signaling? Could they be additive or synergistic in further lowering anxiety?	What is the relationship between FGF2 and GR signaling in nonanxious phenotype during chronic, high-stress conditions?

FGF2, fibroblast growth factor 2; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal.