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# The GDF15-GFRAL Axis in Stress Signalling: A Novel Neuroendocrine Link to Post-Traumatic Stress Disorder (PTSD)

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**Abstract:** ***Post-Traumatic Stress Disorder (PTSD) is a complex neuropsychiatric condition that arises following trauma, yet its biological mechanisms remain poorly defined, complicating the identification of reliable diagnostic markers and effective treatments. Traditional models have focused on dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, but these frameworks often overlook the systemic comorbidities, such as metabolic issues and chronic inflammation, that frequently accompany PTSD. This review proposes an innovative neuroendocrine model centered on the Growth Differentiation Factor 15 (GDF15) and its receptor, GFRAL, suggesting that this pathway is hyperactive in PTSD. GDF15, initially recognized as a marker of metabolic distress, is chronically elevated due to the cellular and metabolic stress induced by severe trauma. Once it enters the central nervous system, GDF15 interacts with GFRAL receptors located in specific brain regions, leading to the activation of neural circuits that contribute to persistent PTSD symptoms, including avoidance behaviors and heightened anxiety. This neuroendocrine pathway serves as a crucial link between the psychological impact of trauma and its physical manifestations. By elucidating the GDF15-GFRAL axis, the review underscores the potential of GDF15 as a biomarker for psychiatric classification and biotype identification. Targeting this pathway through pharmacological or metabolic interventions could represent a promising avenue for developing new therapeutic strategies for PTSD, grounded in a deeper understanding of its biological underpinnings.***

**Keywords:** Post-Traumatic Stress Disorder (PTSD), Growth Differentiation Factor 15 (GDF15), GFRAL Receptor, Stress Signalling, HPA Axis, Biomarker, Cellular Distress

## 1. Introduction

Natural catastrophes, especially floods, create significant physical and psychological stress for affected populations. In addition to the immediate physical injuries, survivors often endure extended periods of nutritional deficiency, exposure to environmental pathogens, and ongoing psychosocial stress. Post-Traumatic Stress Disorder (PTSD) is a complex neuropsychiatric condition affecting a significant number of individuals, often emerging after exposure to traumatic events. It is characterized by a range of symptoms including intrusive memories, avoidance behaviors, negative changes in cognition and mood, as well as heightened arousal. These symptoms can severely impair an individual's daily functioning and quality of life [1]. It is estimated that at approximately 15% following exposure to traumatic events such as combat, sexual assault, or life-threatening accidents [2,3]. PTSD arises from prolonged exposure to stressful circumstances, resulting in enduring sensations of helplessness, profound fear, and terror. Numerous incidents can trigger PTSD, such as physical, mental, or sexual violence in domestic or occupational settings, the sudden demise of a loved one, accidents, warfare, or natural calamities [4]. The World Health Organization estimates the global prevalence of PTSD to be approximately 3.6% [5]. The prevalence of PTSD in disaster-prone regions of India is markedly elevated relative to non-disaster areas. The prevalence of PTSD in India is documented as around 0.2% to 0.24% under typical circumstances [6]; nevertheless, this situation drastically alters after a significant natural disaster. Approximately 70.9% of survivors exhibited signs of PTSD even 4.5 years after the tsunami impacted the Tamil Nadu coast [7]. Diagnosis of PTSD continues to rely primarily on subjective patient reports and clinician-administered scales such as the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and the PTSD Checklist (PCL-5). Despite advances in understanding its psychological framework, the pathophysiological mechanisms remain in complex, and a critical lack of objective biomarkers hampers diagnosis, prognosis, and the development of targeted therapies [8]. Current models focus on dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and fear circuitry, but these do not fully explain the pervasive systemic comorbidities, such as metabolic syndrome and accelerated aging, frequently observed in patients [9]. Nevertheless, the established canonical pathways fall short of comprehensively elucidating the extensive array of somatic symptoms and comorbid conditions, thereby indicating the potential engagement of supplementary, concurrent stress-signaling mechanisms.

Introducing Growth Differentiation Factor 15 (GDF15), which is alternatively referred to as MIC-1 or NAG-1. Initially identified within the framework of macrophage activation, and subsequently associated with cancer-related cachexia, GDF15 has recently undergone a recharacterization as a potent, inducible "stress hormone" or "metabokine." This redefinition underscores its significant role in physiological and pathological processes, highlighting its potential implications in metabolic regulation and stress responses [10]. The expression of this particular entity is significantly enhanced across various tissue types in reaction to a multitude of cellular perturbations, encompassing mitochondrial

dysfunction, oxidative stress, DNA damage, endoplasmic reticulum stress, and inflammatory responses [11,12]. This establishes GDF15 as a pivotal integrator and communicator of cellular distress originating from peripheral tissues. The seminal identification of its distinct, high-affinity receptor, GFRAL, which is predominantly localised within the hindbrain's area postrema (AP) and nucleus tractus solitarius (NTS), has elucidated the previously elusive connection regarding the mechanisms by which this peripheral signal attains preferential entry into the central nervous system circuits that regulate aversion, satiety, and autonomic functions [13].

This review articulates and substantiates a pioneering integrative hypothesis: the GDF15-GFRAL axis represents a critical, hyperactive stress-signaling pathway in the context of post-traumatic stress disorder (PTSD). We put forth the assertion that the significant psychological and physiological disturbances resulting from trauma engender widespread cellular and metabolic stress, which in turn propels a prolonged increase in the levels of circulating GDF15. This enduring hormonal signal, which operates via the hindbrain GFRAL receptor, exerts a significant influence on brainstem circuits that extend projections to critical limbic and hypothalamic regions. Consequently, it plays a direct role in the emergence and persistence of fundamental symptoms associated with post-traumatic stress disorder (PTSD), notably including avoidance behaviours, heightened anxiety, hyperarousal, and interoceptive dysregulation. Moreover, we contend that this axis functions as an essential biological conduit, providing a mechanistic connection between the psychological experience of trauma and its extensively documented somatic comorbidities, which encompass metabolic dysfunction and systemic inflammation. Through the examination of this particular pathway, our objective is to broaden the existing pathophysiological framework of post-traumatic stress disorder (PTSD), underscore its potential in fulfilling the pressing demand for objective biomarkers within the realm of psychiatric classification, and reveal a novel frontier of prospective therapeutic strategies.

## 2. GDF15 Biology: Molecular Mechanisms of a Cellular Distress Beacon

Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor-beta (TGF-β) superfamily, is expressed at significant levels in the placenta and various other organs, including the heart, pancreas, liver, kidney, and colon [14]. Its expression is highly sensitive to cellular stress and is regulated by a network of transcription factors that function as cellular sentinels [15]. The tumor suppressor p53 strongly induces GDF15 gene expression in response to DNA damage and oncogenic stress [16]. Additionally, the integrated stress response (ISR) pathway, which is activated by conditions such as amino acid deprivation, viral infection, or heme deficiency, triggers the phosphorylation of eukaryotic initiation factor 2α (eIF2α) and leads to the translation of the transcription factor ATF4, ultimately resulting in the upregulation of GDF-15 [17].

GDF-15 secretion was further stimulated by some pro inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α reinforcing its role as a downstream mediator in inflammatory signalling [18,14]. After synthesis of GDF-15 protein, is cleaved by proprotein convertases and subsequently produce a 25 KDa mature, and which eventually enters the systemic circulation [19]. The central action of GD-15 was enigmatic due to lack of identified receptor in brain, and which was eventually resolved by the discovery of GFRAL receptor. GFRAL, is a member of GDNF receptor family, acts specifically on catecholaminergic neurons within the area postrema (AP) and the nucleus tractus solitarius (NTS) [20]. AP and NTS are the “windows of the brain”. circumventricular organ characterized by a porous blood-brain barrier, which enables it to sample molecules present in the blood. In contrast, the NTS serves as the primary viscerosensory nucleus that receives input from vagal and glossopharyngeal afferents. GFRAL forms a functional receptor complex with the RET tyrosine kinase [21]. When GDF15 binds to this complex, it induces RET dimerization and autophosphorylation, which activates downstream signaling cascades. These cascades primarily involve the MAPK/ERK and PI3K/AKT pathways, leading to neuronal activation and adaptive transcriptional changes [22].

The primary pathway of the activated GFRAL neurons projected to the lateral parabrachial nucleus (PBN) [23]. PBN act as a major relay station that disseminates interoceptive information to forebrain structures involved in affect, motivation, and learning [24]. Signals arises from PBN, transmitted to the central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and hypothalamic nuclei, which ultimately connecting this peripheral stress-sensing system to the core neural substrates of emotional valence, fear, anxiety, and homeostatic regulation [25]. This well-defined neuroanatomical architecture provides a direct conduit for a blood-borne metabolic stress signal to influence complex emotional and behavioral states.

## 3. The GDF15-GFRAL Axis as a Direct Conduit for Trauma-Related Pathophysiology

Psychological trauma not only a subjective experience but also bring out intense and multisystemic biological response. Persistence trauma is associated with elevated oxidative stress, mitochondrial bioenergetic deficits, elevated markers of cellular senescence (e.g., shortened telomeres), and a persistent, low-grade inflammatory state characterized by elevated cytokines like IL-6 and TNF-α [26]. The concept of "biological scarring" suggests that allostatic load significantly contributes to persistent GDF15 elevation in PTSD, indicating chronic physiological deterioration.

Several core and comorbid conditions which are associated with PTSD, theoretically linked with elevated GDF-15 signalling via hindbrain GFRAL receptor. This was happened by various discrete but interconnected mechanisms:

- **Potentiation of Conditioned Avoidance and Aversive Learning:** The canonical mediator of the conditioned taste aversion (CTA) is the GDF15-GFRAL pathway [27], a type of cognitive development where an animal learns to avoid a new sensation that makes them uncomfortable. In the context of PTSD, persistently elevated GDF-15 signalling could reduce the threshold for establishing negative psychological association [28], prolong adverse

learning beyond the initial trauma trigger, and eventually promote the avoidance behaviour – a core diagnostic criteria.

- **Driving Autonomic and Visceral Dysregulation:** Persistent GDF15-GFRAL signaling could disrupt the sympathetic neurones [29], contributing to the cardiovascular instability [30], gastrointestinal complaints [31], and respiratory dysregulation [32] commonly reported in PTSD patients.
- **Bidirectional Interaction with Inflammation and the HPA Axis:** GDF15 both responds to and can modulate inflammatory processes [14]. In PTSD, it may act within a feed-forward loop, where inflammation drives GDF15, which in turn may prime immune cells or alter the brain's inflammatory milieu [33,14]. The dense neural connection from the NTS to the PVN regulates both acute and chronic HPA axis responses, as well as adrenal sensitivity, to various types of stressors (systemic and psychogenic) primarily through catecholaminergic (NE) and neuropeptide (GLP-1/PrRP) signalling [34]. Altered GDF15 signaling could therefore indirectly influence CRF release and glucocorticoid dynamics, potentially contributing to the atypical HPA profile observed in PTSD [35].

Critically, the GDF15-GFRAL axis can be conceptualized as a **"Physical Stress Pathway" that is co-opted by severe psychological trauma**. While the classical HPA axis is exquisitely tuned to psychological and anticipatory stressors, the GDF15 system appears more responsive to direct cellular/metabolic insults (e.g., tissue injury, hypoxia, nutrient deprivation). We hypothesize that extreme psychological trauma, through mechanisms like catecholamine surge, oxidative burst, and immune activation, creates a systemic physical stress state robust enough to chronically engage this pathway, blurring the line between psychological and physical threat at a biological level.

## 4. Clinical Evidence, Biomarker Potential, and the Quest for Biological Subtyping

Empirical support for this model is accumulating from human studies. One of the previous review study shows that serum GDF-15 level was elevated in chronic and acute psychological stress [28]. One of the previous study shows that plasma GDF15 levels were found to be significantly and positively associated with the severity of depressive symptoms in women [36].

This growing evidence base positions GDF15 as a leading candidate for a desperately needed **objective biomarker in PTSD**. Current diagnostic practices rely entirely on subjective symptom report via clinical interviews (e.g., the Clinician-Administered PTSD Scale, CAPS-5) and self-report questionnaires (e.g., PTSD Checklist for DSM-5, PCL-5). This approach, while essential, is susceptible to recall bias, symptom minimization or exaggeration, cultural variation in symptom expression, and the challenge of differential diagnosis given high rates of comorbidity (e.g., with major depression, generalized anxiety). The field of psychiatry is urgently moving towards a precision medicine framework, which requires the identification of biologically distinct subgroups, or **biotypes**, within a heterogeneous diagnostic category like PTSD.

In this context, GDF15 measurement could serve multiple transformative functions:

1) **Diagnostic Adjunct:** Providing a quantitative, biological measure to supplement and validate clinical assessment, improving diagnostic accuracy.
2) **Biotype Identification:** Helping to stratify PTSD patients into subgroups, such as a "high cellular stress/metabolic" biotype characterized by elevated GDF15, inflammation, and prominent somatic comorbidities, which may have a distinct prognosis and respond preferentially to specific interventions (e.g., anti-inflammatory or metabolic treatments).
3) **Treatment Response Trajectory:** Serving as an objective, pharmacodynamic biomarker to monitor biological response to therapy (e.g., psychotherapy, pharmacotherapy, neuromodulation) independent of symptom self-report.
4) **Risk and Resilience Stratification:** In prospective studies of trauma-exposed populations (e.g., first responders, military personnel), serial GDF15 measurements could help identify individuals whose biological stress response remains dysregulated, signaling higher risk for developing chronic PTSD and necessitating early preventive intervention.

Realizing this potential requires rigorous, longitudinal cohort studies that measure GDF15 alongside deep phenotyping (psychometrics, autonomic measures, neuroimaging, genomics) from the acute post-trauma period through long-term follow-up.

## 5. Therapeutic Implications: From Novel Targets to Integrated Interventions

The delineation of the GDF15-GFRAL axis opens unprecedented avenues for therapeutic innovation in PTSD, moving beyond serotonin reuptake inhibitors and trauma-focused psychotherapies.

1) **Pharmacological Targeting:** The most direct approach involves developing agents that modulate this specific pathway. **GFRAL antagonists** or **monoclonal antibodies that neutralize circulating GDF15** are already in clinical development for conditions like cancer cachexia and obesity (Suriben et al., 2020). Repurposing these agents for psychiatric indications offers a promising strategy. A GFRAL antagonist could, in theory, block the downstream neural effects of chronic GDF15 elevation, potentially reducing avoidance, anxiety, and visceral distress without altering the hormone's peripheral protective or metabolic functions. Clinical trials would need to carefully evaluate efficacy on PTSD symptom clusters and monitor for potential metabolic side effects, such as weight gain.
2) **Lifestyle and Metabolic Interventions:** Given that GDF15 is a metabolic stress signal, interventions that improve overall metabolic health and cellular resilience may beneficially modulate this axis. Regular aerobic exercise acts as a dual regulator; while an acute bout of exercise triggers a transient, physiological spike in circulating GDF15 to assist in systemic energy

homeostasis [38], sustained physical training over time promotes mitochondrial biogenesis and reduces chronic systemic inflammation, thereby lowering pathological, baseline GDF15 tone. Complementary dietary strategies, such as time-restricted feeding or regimens rich in polyphenols and omega-3 fatty acids, can further mitigate oxidative stress and enhance metabolic flexibility, potentially exerting a stabilizing influence on the GDF15-GFRAL system [39]. Consequently, these non-pharmacological interventions could serve as powerful, low-risk adjuncts to standard PTSD treatment protocols.

3) **Combination Strategies:** Future treatment paradigms may involve combining GFRAL-targeted biologics with psychotherapy. By pharmacologically reducing the aversive interoceptive state and lowering the threshold for avoidance, a GFRAL antagonist might theoretically enhance engagement with and tolerance for exposure-based therapies, which are often limited by high dropout rates due to the distress they provoke.

## 6. Future Directions, Unanswered Questions, and Conclusion

While the GDF15-GFRAL axis presents a compelling new framework, it remains a nascent field of inquiry in psychiatry, ripe with unanswered questions and directions for future research:

1) **Causal Mechanistic Studies:** There is a pressing need for direct causal evidence. Preclinical studies using established rodent models of PTSD (e.g., single prolonged stress, chronic variable stress) must investigate whether: a) trauma paradigms increase central and peripheral GDF15, b) genetic or pharmacological blockade of GDF15 or GFRAL prevents or reverses trauma-induced behavioral and physiological deficits, and c) exogenous GDF15 administration is sufficient to induce PTSD-relevant behaviors in naïve animals.
2) **Circuit-Level Precision:** Advanced neuroscience techniques (e.g., in vivo calcium imaging, optogenetics, chemogenetics) should be employed to map the specific populations of $GFRAL^{+}$ neurons in the AP/NTS that are activated by stress, define their precise projection patterns to the PBN and beyond, and elucidate how their activation alters neural activity in downstream limbic targets.
3) **Human Translational Neuroscience:** Neuroimaging studies in PTSD patients should explore correlations between peripheral GDF15 levels and functional connectivity of the brainstem (NTS/PBN) with the amygdala and insula—key regions for interoception and threat processing. The development of GFRAL-specific PET ligands, though challenging, would be a revolutionary tool for quantifying receptor availability in the living human brain.
4) **Interaction with Other Systems:** Research must explore how this axis interacts with other key players in PTSD, including the gut microbiome (which can influence systemic GDF15), neuroinflammation (microglial activation), and other stress-responsive hormones (e.g., ghrelin, leptin).
5) **Longitudinal Biomarker Validation:** Large-scale, multi-site longitudinal studies, such as the AURORA study, provide an ideal platform to prospectively validate GDF15 as a predictive and prognostic biomarker, integrating it with other omics data (genomics, proteomics, metabolomics) to build comprehensive risk models.

In conclusion, the GDF15-GFRAL axis represents a paradigm-shifting discovery in stress biology with profound implications for understanding PTSD. It provides a elegant and testable mechanism for how the psychological experience of trauma becomes biologically embedded, disrupting not only brain circuits of fear and emotion but also systemic metabolic and inflammatory homeostasis. By forging a direct link between peripheral cellular distress and central affective circuits via a dedicated hindbrain gateway, this axis offers a unifying explanation for the co-occurrence of psychological and somatic symptoms in PTSD. As research advances, this pathway holds immense promise for transforming the clinical landscape—ushering in an era of objective biomarker-driven diagnosis, biologically defined subtyping, and novel, mechanism-based therapeutics that target the deep physiological roots of traumatic stress. The investigation of the GDF15-GFRAL axis is not merely an additive endeavor but a necessary step towards a more holistic, integrative, and effective biopsychosocial model of PTSD.

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