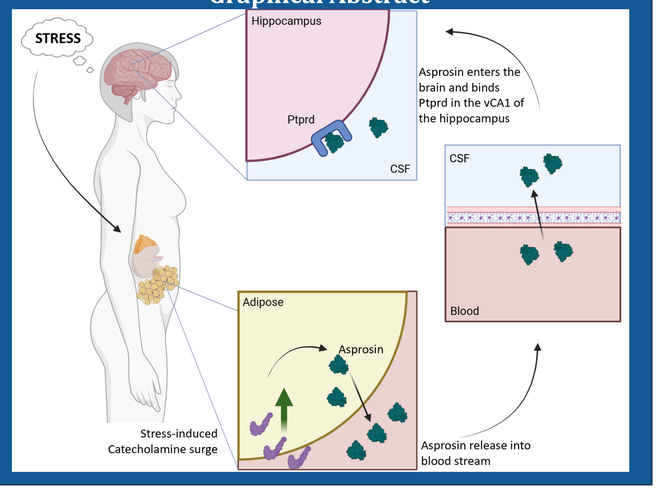
# A hormone circuit from fat to hippocampus drives a novel, druggable anxiety pathway

Bijoya Basu[1], Qianru Zhao[2], Hiba Obeid[1], Yanlin He[2], Atul Chopra[1,]
[1]Case Western Reserve University, Cleveland, OH, [2]Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA

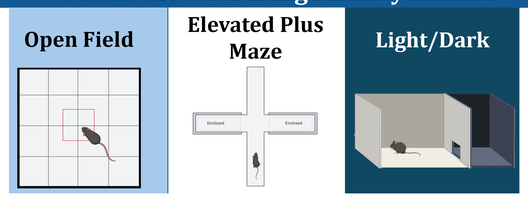
## Graphical Abstract




## Introduction

- Anxiety is an ancient survival mechanism that enhanced vigilance and escape from threats, but in today's world of chronic stress, it often becomes pathological.
- Nearly one in three people experience an anxiety disorder in their lifetime, yet current treatments remain limited, with low remission rates and significant side effects.[1]
- Most available drugs act on serotonin, dopamine, or GABA systems, leaving a critical need for therapies that target fundamentally different mechanisms. [2]
- We discovered that the metabolic hormone asprosin [3], secreted by fat tissue, drives anxiety by acting on its receptor Protein Tyrosine Phosphatase Recptor Delta (Ptprd) [4] in hippocampal circuits.
- This adipose-to-brain signaling pathway represents a previously unrecognized link between metabolism and emotion, opening new avenues for anxiolytic drug development.

## Methods: Measuring Anxiety in Mice




Anxiety-like behavior was quantified across well-validated assays: open field, light–dark, and elevated plus maze, under multiple conditions.

We manipulated the asprosin-Ptprd signaling axis in mice using five approaches: (1) viral overexpression of asprosin (Ad5-FBN1 or AAV8-asprosin); (2) genetic loss-of-function models, including $Fbn1^{NPS/+}$ mice (asprosin-deficient) and $Ptprd^{+/-}$ mice (3) peripheral neutralization with an anti-asprosin monoclonal antibody (mAb[5]); (4) pharmacologic inhibition of asprosin receptor (5) stereotactic Cre-mediated deletion of Ptprd in specific brain regions.

## Results

### 1 Asprosin bi-directionally modulates anxiety, regardless of metabolic state

**Figure 1:**

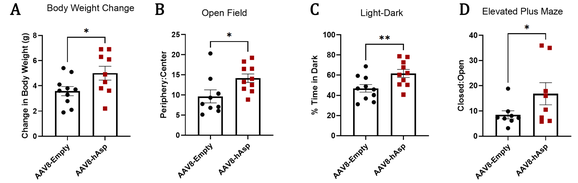



**Figure 2:**

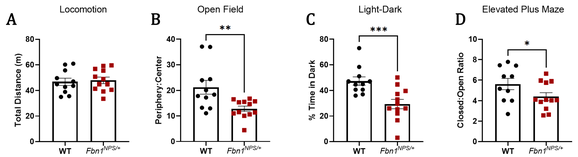



**Figure 3:**

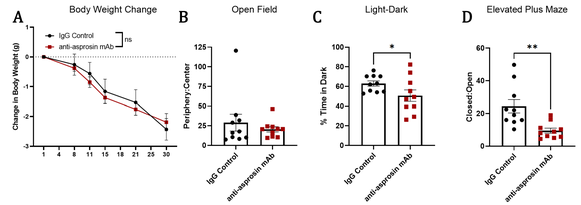



**Figure 1:** Body weight change **(A)**, Open Field assay Periphery:Center time **(B)**, Light-Dark assay Percent Time in Dark **(C)**, and Elevated Plus Maze assay Closed:Open arm time **(D)** between 20 week old mice injected with AAV8-Empty and AAV8-hAsp at 12 weeks (n = 9-10/group) show more anxiety in AAV8-Asprosin group; **Figure 2:** Distance traveled **(A)**, Open Field assay Periphery:Center time **(B)**, Light-Dark assay Percent Time in Dark **(C)**, and Elevated Plus Maze assay Closed:Open arm time **(D)** between 12-week old male $Fbn^{NPS/+}$mice and age-matched WT littermates (n = 10-12/group), shows $Fbn^{NPS/+}$mice to have less anxiety; **Figure 3:** Body weight change measured over 30 days **(A)**; Open Field assay Periphery:Center time **(B)**, Light-Dark assay Percent Time in Dark **(C)**, and Elevated Plus Maze assay Closed:Open arm time **(D)** between 6-month old lean male mice treated once daily intraperitoneal injection of anti-asprosin mAb and isotype-matched IgG control (n=10/group) shows asprosin neutralization decreases anxiety

### 2 Genetic inhibition of asprosin receptor results in a decrease in anxiety

**Figure 4:**

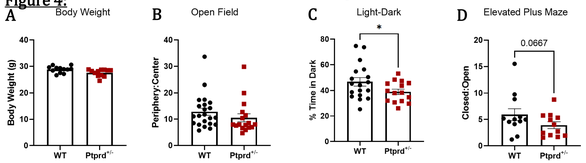



**Figure 4**: Body weight change **(A)**, Open Field assay Periphery:Center time **(B)**, Light-Dark assay Percent Time in Dark **(C)**, and Elevated Plus Maze assay Closed:Open arm time **(D)** between 10-week old male Ptprd+/ mice (n=12-22/group) shows heterozygous mice are less anxious

### 3 Induced anxiety is treated by asprosin neutralization

**Figure 5:**

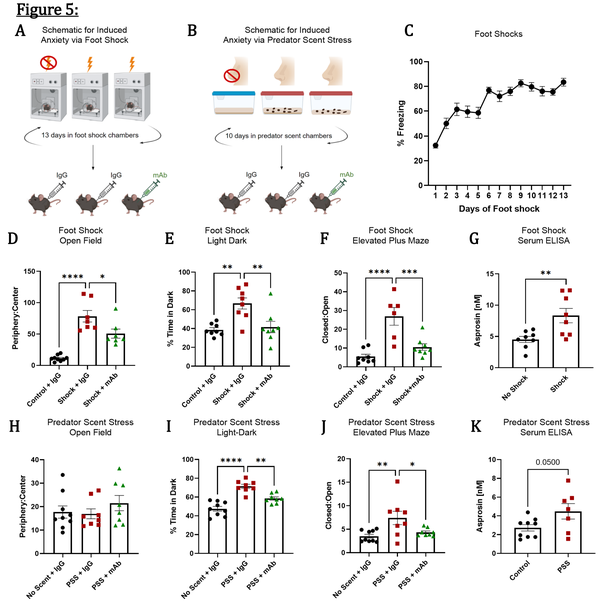



**Figure 3**: **(A-B)** Experimental paradigms: induced anxiety via foot shock **(A)** or predator scent stress (PSS) **(B)**, followed by treatment with anti-asprosin mAb (150 µg/mouse) or IgG control. **(C)** Freezing behavior in foot shock–exposed mice before antibody treatment (n=16). **(D-F)** Anxiety-like behavior after foot shock, assessed by Open Field (Periphery:Center), Light–Dark (time in dark), and Elevated Plus Maze (Closed:Open arms) in controls, IgG, and anti-asprosin mAb groups (n=6–9). **(G)** Serum asprosin levels in foot shock vs controls (n=8/group). **(H-J)** Anxiety-like behavior after PSS, measured by the same three assays in controls, IgG, and anti-asprosin mAb groups (n=8–9). **(K)** Serum asprosin levels in PSS vs controls (n=7–9).

### 4 Catecholamine surges cause an increase in asprosin release

**Figure 6:**

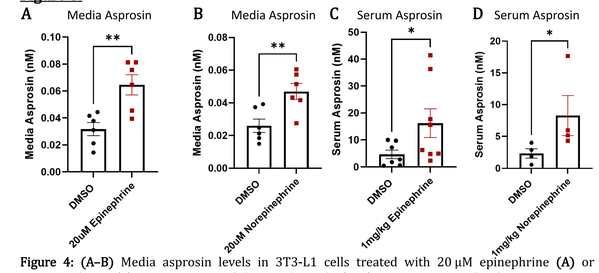



**Figure 4: (A–B)** Media asprosin levels in 3T3-L1 cells treated with 20 µM epinephrine **(A)** or norepinephrine **(B)** vs DMSO control (n=5–6/group). **(C–D)** Serum asprosin levels in mice 5 min after 1 mg/kg epinephrine **(C)** or norepinephrine **(D)** via intraperitoneal injection compared to vehicle (n=8/group).

### 5 Asprosin binds to the vAC1 regions of the hippocampus to modulate anxiety

**Figure 7:**

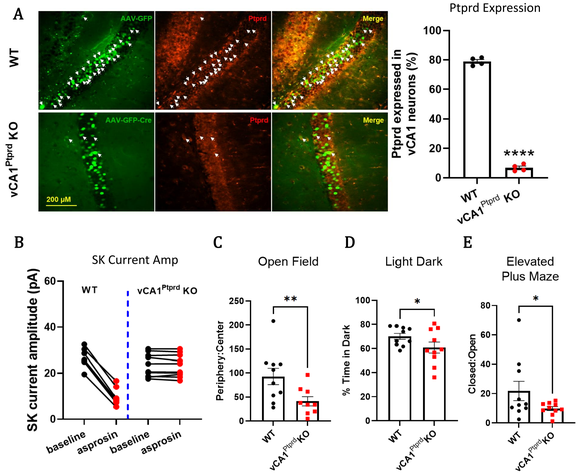



**Figure 5: (A)** Representative image of immunostaining of AAV virus (green) and Ptprd (red) of vCA1Ptprd KO mice and WT adult male mouse using fluorescence microscopy **(B)** Ptprd expression in vCA1 neurons in WT mice or vCA1Ptprd KO mice **(C-E)** Open Field assay Periphery:Center time **(C)**, Light-Dark assay Percent Time in Dark **(D)**, and Elevated Plus Maze assay Closed:Open arm time **(E)** comparing male WT with age- and sex-matched $vCA1^{Ptprd}$KO (n =9-10/group) show KO mice have less anxiety

## Discussion

Anxiety disorders affect nearly one-third of the population, yet current treatments remain inadequate. SSRIs and SNRIs fail in many patients and often cause adverse effects, while benzodiazepines introduce risks of dependence and addiction[1,2]. This gap highlights the urgent need for mechanistically distinct therapies.

We identify asprosin, a fasting-induced adipokine[3], as a key driver of anxiety through its neuronal receptor Ptprd[4]. Elevated asprosin directly enhances excitability of ventral hippocampal pyramidal neurons, promoting anxiety-like behavior. Genetic deficiency or antibody-mediated neutralization of asprosin markedly reduces anxiety across preclinical models, while increasing circulating asprosin intensifies it. Disrupting Ptprd mirrors these anxiolytic effects, confirming the centrality of this axis. Finally, we find that catecholamines directly cause asprosin release showing how this circuit is activated in states of heightened anxiety.

Our findings validate asprosin-Ptprd signaling as an adipose-to-brain signaling circuit regulating emotional state. Targeting this pathway offers a transformative, non-monoaminergic strategy for next-generation anxiolytic development.

## References

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