

# The metabolic footprint of the Short Unpredictable Variable Stress model in male Wistar rat

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## HIGHLIGHTS

The Short Unpredictable Variable Stress (SUVS) is proposed as a pilot model of rodent anxiety.

Plasma and urine metabolomics provide a characteristic omic profile.

11 metabolites are considered candidate biomarkers for the anxiety model making part of the metabolic footprint of the disorder.

## RESULTS

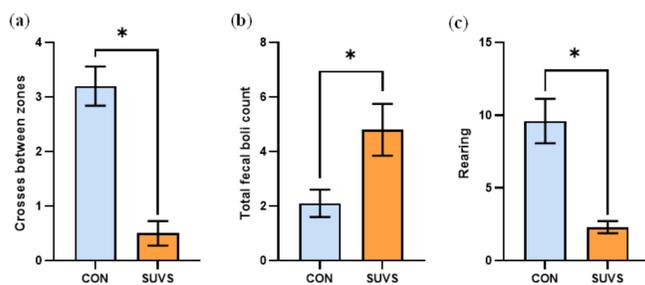


Figure 1. Anxiety-like behaviour on the OFT test. CON (n = 10) and SUVS (n = 10) rats were subjected to the OFT during 5 min. (a) Number of crosses between inner and outer zone. (b) Total number of fecal boli deposits. The number of defecations was manually counted by the observer after rats were removed. (c) Rearing behaviour. The statistically significant p-values versus CON (p < 0.05) are highlighted with an asterisk (\*).

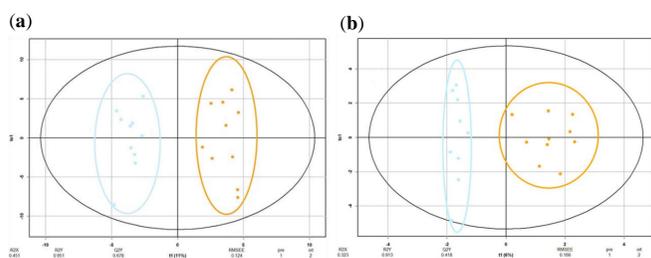


Figure 2. OPLS-DA of plasma (a) and urine metabolomics (b). Blue represents CON group and orange SUVS group. The Score plot is represented, and it includes the number of components, the cumulative R2X, R2Y and Q2Y.

23 metabolites in plasma and 3 in urine were significantly altered that reflected the anxiety disturbed pathways, which are mainly involved in energy and lipid metabolisms, characterized by disturbed tricarboxylic acid (TCA) cycle and fatty acid degradation, and neurotransmitter synthesis. Specifically, 8 metabolites in plasma were considered potential biomarkers of anxiety including succinic acid, malic acid, threonic acid, alpha-ketoglutarate, pyruvic acid, cholesterol, oleic acid and 3-hydroxybutyric acid; and 3 metabolites in urine including N,N-dimethylglycine, taurine and methylamine.

## DISCUSSION

Differences between the anxiety and control group were observed in behavior, biochemical determinations, and metabolic patterns providing a metabolic footprint of the SUVS model. The main metabolic pathways altered in the SUVS group were glycolysis, amino acid metabolism, lipid metabolism, methylamine metabolism and TCA cycle. Additionally, more studies profiling anxiety are recommended for further exploration and validation of the metabolic footprint.

## INTRODUCTION

Anxiety disorders have increased dramatically in recent decades becoming the most prevalent psychiatric disorder in the United States and Europe. However, anxiety disorders are complex conditions, with not fully understood pathology mechanisms. Numerous factors, including psychological, genetic, biological, and chemical factors, are thought to be involved in their etiology. The diagnose of anxiety disorders is currently based on symptom checklist and psychological questionnaires, making the identification of biomarkers of anxiety necessary to gain better insights into patient-specific pathology mechanisms that lead to the properly diagnose and treatment. Among potential biomarkers, metabolic profiling seems promising to recognize early biochemical changes in disease and provides an opportunity to develop predictive biomarkers that can initiate earlier interventions. Here, we studied plasma and urine metabolites in the Short Unpredictable Variable Stress (SUVS) animal model, which aims to mimic a short anxiety period.

## METHODS

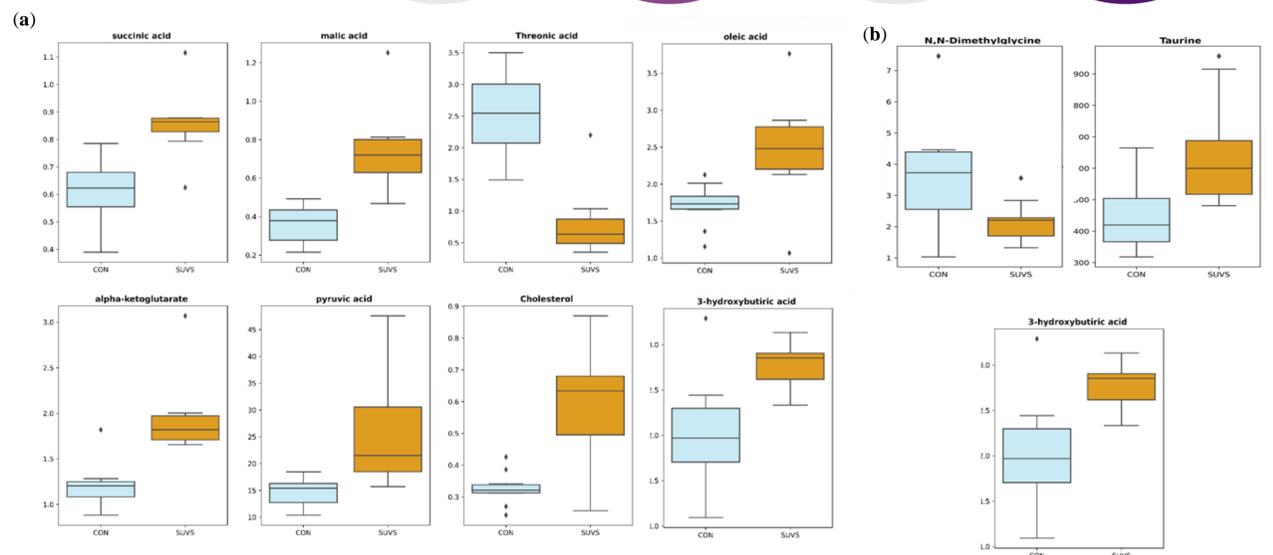
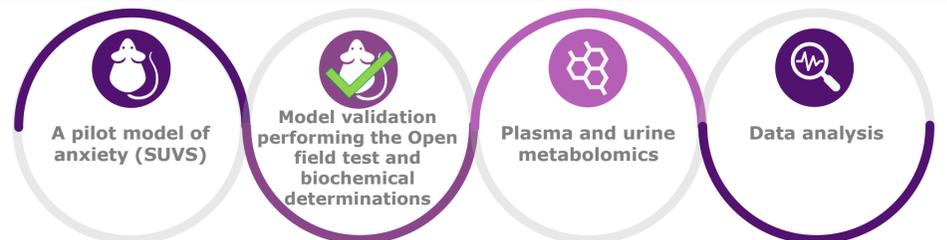


Figure 3. Box-whisker plots of the metabolites that distinguish between CON and SUVS groups. (a) Plasma metabolites (b) Urine metabolites. Blue represents CON group and orange SUVS group. Box denotes 25th and 75th percentiles; line within box denotes 50th percentile (median); whisker denotes standard deviation.

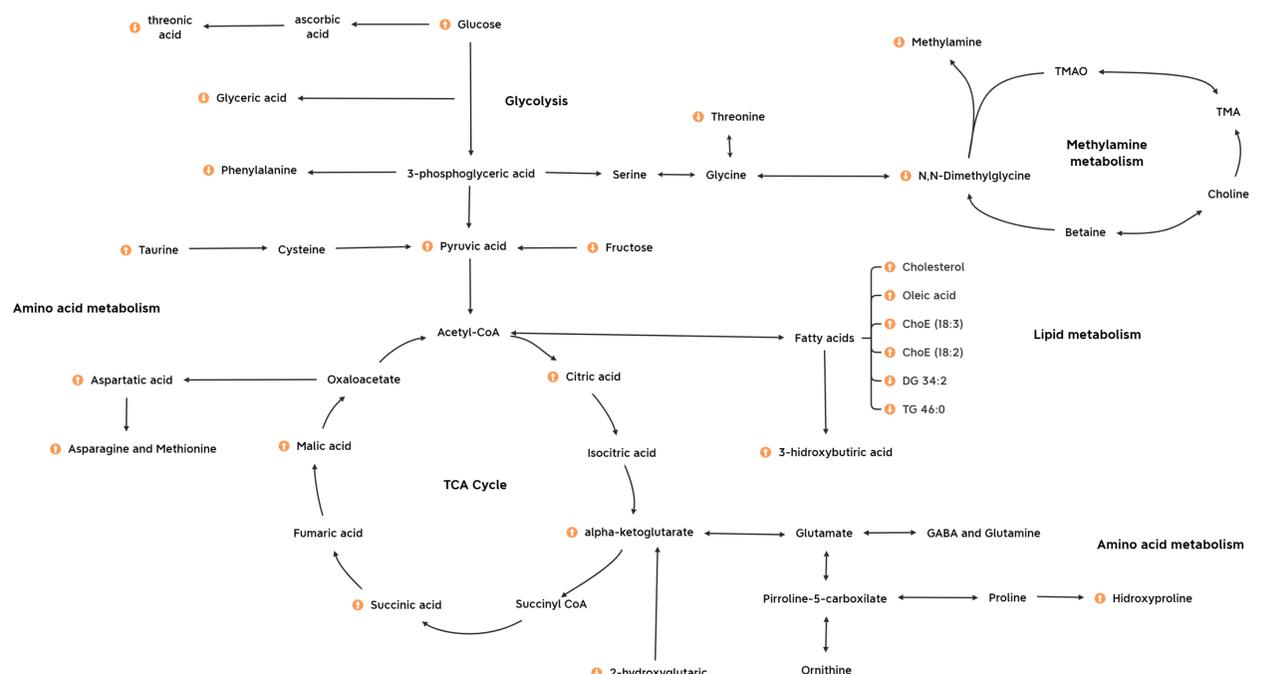


Figure 4. Metabolic profiling of candidate biomarkers and the main metabolic pathways implicated in the anxiety model. The up and down regulated metabolites are indicated with up and down arrows. Abbreviations: DG, diacylglycerol; ChoE, cholesterol ester; TG, triglyceride; TMAO, trimethylamine N-oxide; TMA, trimethylamine; GABA, gamma aminobutyric acid.

## REFERENCES

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