Exploring the role of sphingolipid metabolism in the vulnerability and resilience to stress-induced anhedonia in the CMS model of depression

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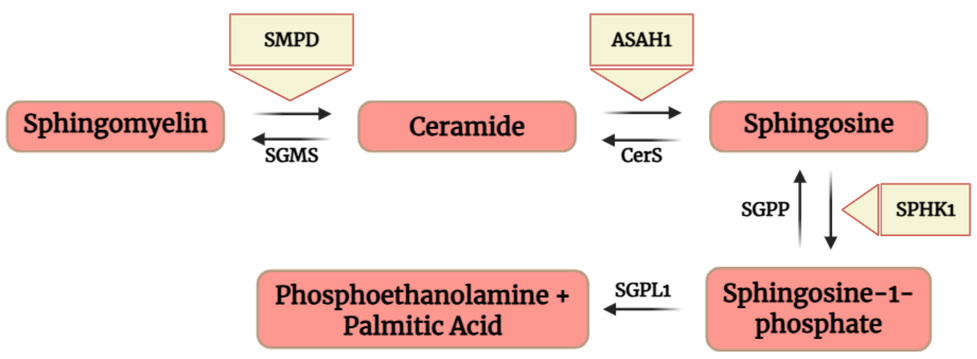
Background

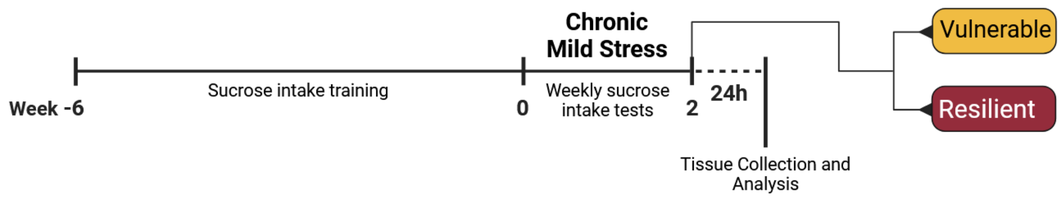
Stress is a key environmental risk factor for **major depressive disorder (MDD)**, yet its effects differ: most individuals show resilience, while a minority develop stress-related psychopathologies requiring treatment. Identifying the molecular bases of **resilience** and **vulnerability** is crucial for new therapies. The sphingomyelin metabolism pathway, initiated by hydrolysis of sphingomyelin into ceramide, is increasingly implicated in MDD. Using a chronic mild stress (CMS) model of depression to mimic anhedonia, a core symptom of the disease, we investigated this pathway and found preliminary evidence that resilience may rely on better regulation of sphingolipid metabolism, favoring neuroprotective over neurotoxic products such as ceramide.



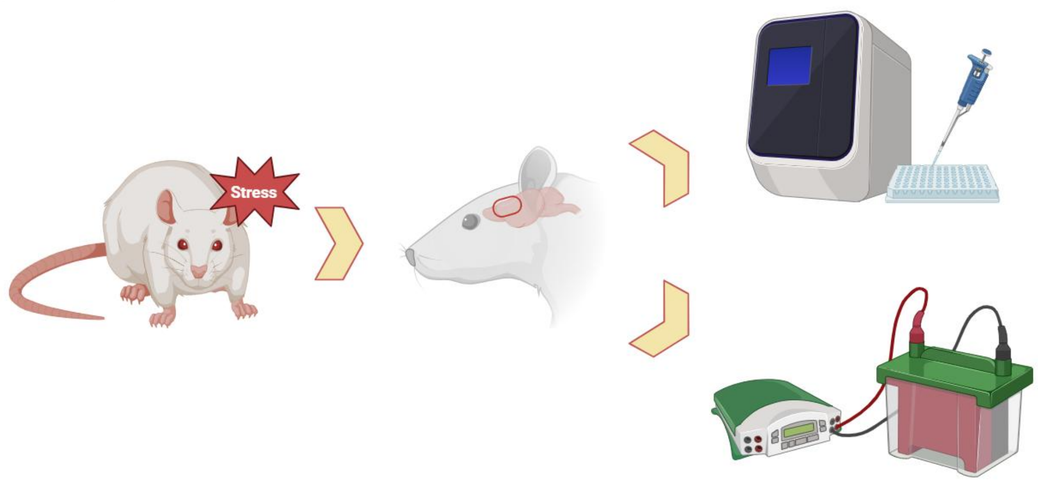
Aim

To investigate whether stress-induced changes in sphingomyelin metabolism contribute to resilience or vulnerability in the chronic mild stress (CMS) model of depression.

Methods

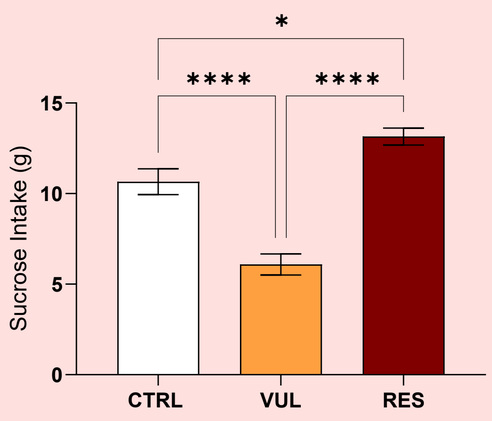


Adult male rats were first trained for sucrose intake test to establish baseline consumption (week –6 to 0). Animals were then exposed to a 2-week **chronic mild stress (CMS)** paradigm, during which sucrose intake was monitored weekly. Based on the sucrose intake test, stressed animals were classified as either **resilient** (no reduction in sucrose intake) or **vulnerable** (significant reduction, indicative of anhedonia). Twenty-four hours after the last stressor, rats were sacrificed and prefrontal cortex was collected for protein and gene expression analyses of key elements of the sphingolipid metabolism pathway.

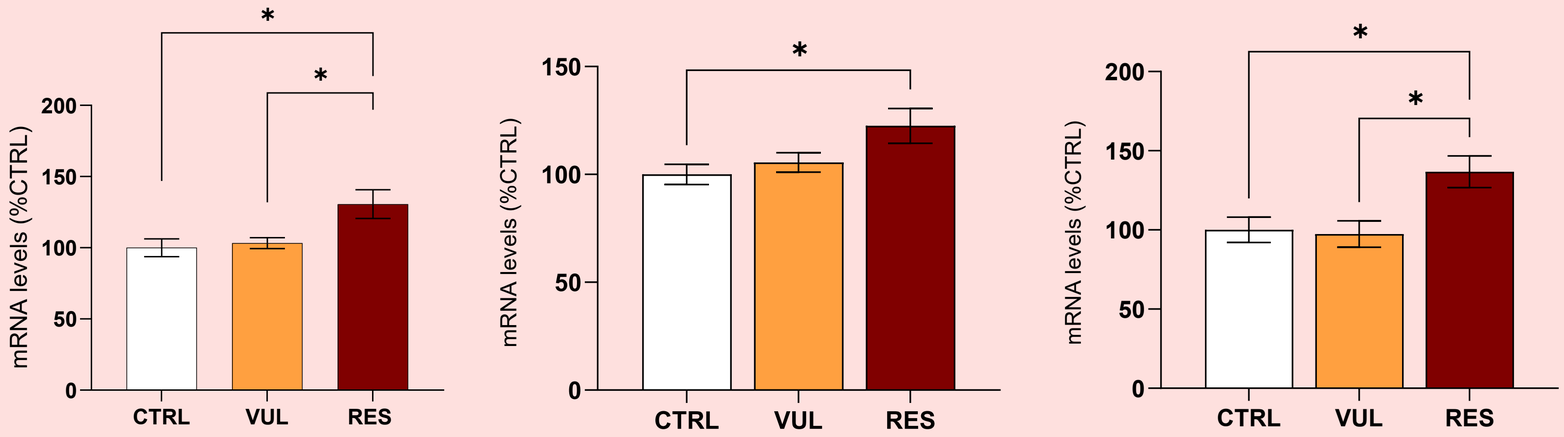


Results

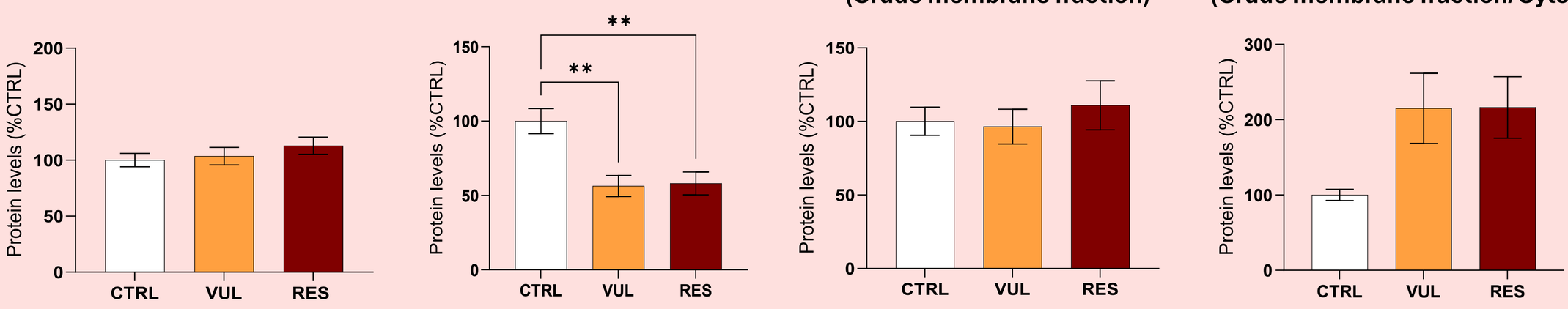
BEHAVIOR ANALYSIS



GENE EXPRESSION ANALYSIS



PROTEIN LEVEL ANALYSIS



****P<0.0001; **P<0.01; *P<0,05. One-Way ANOVA with Tukey post-hoc test

Conclusions

- **The increased gene expression of *SMPD2*, *ASAH1*, and *SPHK1* in resilient rats** may indicate enhanced activation of the pathway leading to sphingosine-1-phosphate (S1P) production, a lipid mediator reported in the literature as protective and pro-survival [1].
- **The stress-induced reduction of cytosolic SPHK1** could reflect the translocation of its active form to membranes, where it phosphorylates sphingosine to S1P.

These observations warrant further investigation to better understand the role of sphingolipid metabolism in the mechanisms of resilience to chronic stress. Such insights could ultimately help identify novel therapeutic targets for stress-related psychopathologies.

Future perspectives

Future studies will extend these findings by quantifying **S1P** and **ceramide** levels to provide a clearer lipidomic profile. Given the emerging role of the S1P receptor **S1PR3** in stress resilience [2], its potential involvement will be investigated to better elucidate the contribution of S1P signaling to adaptive responses under chronic stress.

References

[1] Czubowicz, K. & Strosznajder, R. Ceramide in the Molecular Mechanisms of Neuronal Cell Death. The Role of Sphingosine-1-Phosphate. Mol Neurobiol 50, 26–37 (2014).

[2] Corbett, B. F. et al. Sphingosine-1-phosphate receptor 3 in the medial prefrontal cortex promotes stress resilience by reducing inflammatory processes. Nat Commun 10, (2019).

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