Depression and Astrocyte Metabolism: Lactate Production in the ACC and Its Impact on Brain Energy Regulation

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Introduction

Major Depressive Disorder: A Global Crisis

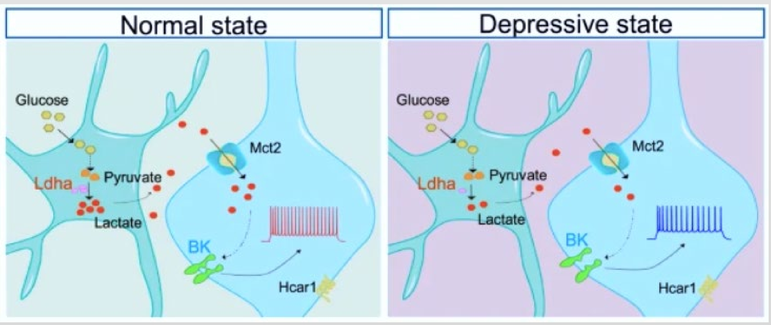
- Over 280 million people worldwide
- Leading cause of disability
- Over 700,000 suicide deaths annually
- Up to 30% of patients remain symptomatic despite treatment[1]

Astrocytes

- Key glial cells that support brain metabolism and energy balance by producing lactate via enzyme lactate dehydrogenase A (LDHA)[2]
- Chronic stress disrupts glucose metabolism, weaking brain energy supply[3]

Astrocyte-Neuron Lactate Shuttle Hypothesis

Activation of nerve cells leads to glutamate release, which is actively taken up into astrocytes by transporter (GLT-1) and converted into glutamine. Pyruvate is converted to lactate by (LDHA) and exported out of the cell by transporter 1 or 4 (MCT1/4) and transported into nerve cells via MCT2.[3]



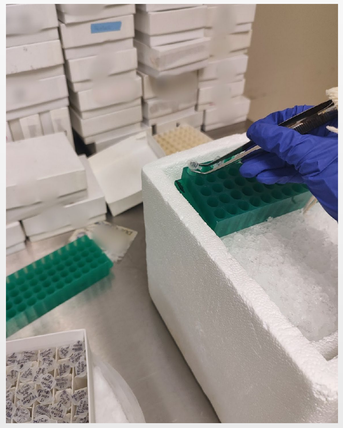
Anterior Cingulate Cortex

- Central to emotional regulation and cognition
- Energy deficits from impaired astrocytic lactate production, disrupts synaptic plasticity, memory, and cognition[4]
- ACC dysregulation correlates with poorer treatment outcomes in MDD[5]

AIM: To determine whether altered LDHA expression in the anterior cingulate cortex contributes to impaired lactate production and energy deficits in MDD

Materials and Methods

- **Sample**: MDD (24) and control (12) post-mortem brain samples of the anterior cingulate cortex.
- **Procedures:** mRNA expression was quantified by qPCR. Normalization was quantified by geometric averaging of reference genes (GAPDH, TBP, UBC).
- **Statistical Analysis**: Between-group differences were investigated using SPSS.



Clinical and Demographic Data

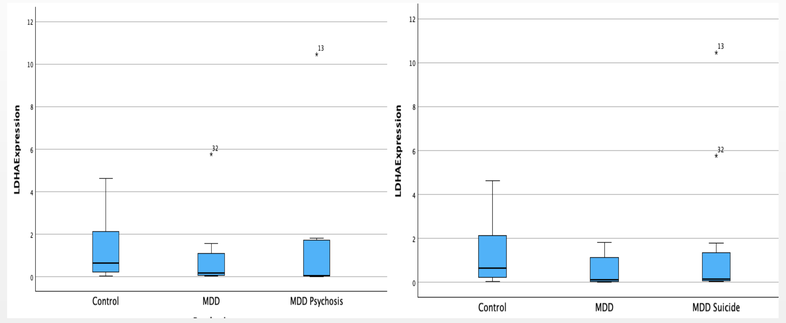
	CON (n=12)	MDD (n=24)
Age (years)	46.8±16.2	42.2±20.8
PMI (hours)	25.2±14.8	29.7±35.3
Brain pH	6.6±0.3	6.6±0.3
Sex (F:M)	4:8	11:13
Cause of Death		suicide/hanging n=8
		suicide/overdose n=5
		suicide/gunshotwound n=2
		suicide/stabbed n=1
		suicide/jumped n=1
	cardiac n=7	cardiac n=3
	acute alcohol poisoning n=1	overdose n=1
	obesity n=1	pulmonary embolism n=1
	motor vehicle accident n=3	burns n=1
		other n=1
Psychosis (no:yes)	NA	12:12
Age of Onset (years)	NA	29.9±29.1
Illness Duration (years)	NA	12.3±18.7

Results

LDHA expression levels tend to be higher in controls compared to those with depression (p=0.254).

However, the difference is not statistically significant across psychosis and suicide groups with depression relative to CON (p= 0.430) and (p=0.380).

Age, PMI, pH, sex, age of onset, and duration of illness did not impact gene expression.



Conclusions and Future Steps

- **Findings**: While previous studies in the dmPFC show reduced LDHA protein[3], our analysis in the ACC revealed no significant difference in LDHA mRNA expression between depression and control groups. This suggests possible post-transcriptional regulation or region-specific differences in astrocytic metabolism.
- **Limitations**: The limited sample size may reduce the ability to detect relevant differences in LDHA expression, highlighting the need for further research to confirm these findings.
- **Functional Implications**: Future studies should examine extracellular lactate levels and neuronal excitability in the ACC to determine if lactate metabolism is disrupted despite unchanged mRNA levels.

References

[1] WHO Depressive Disorder. 2023. [2] Chen et al. 2022 PMID: 37861858

[3] Yao et al. 2023 PMID: 36759610. [4] Akter et al. 2023 PMID: 37960975.

[5] Leonards et al. 2024 PMID: 38218081

Acknowledgements

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