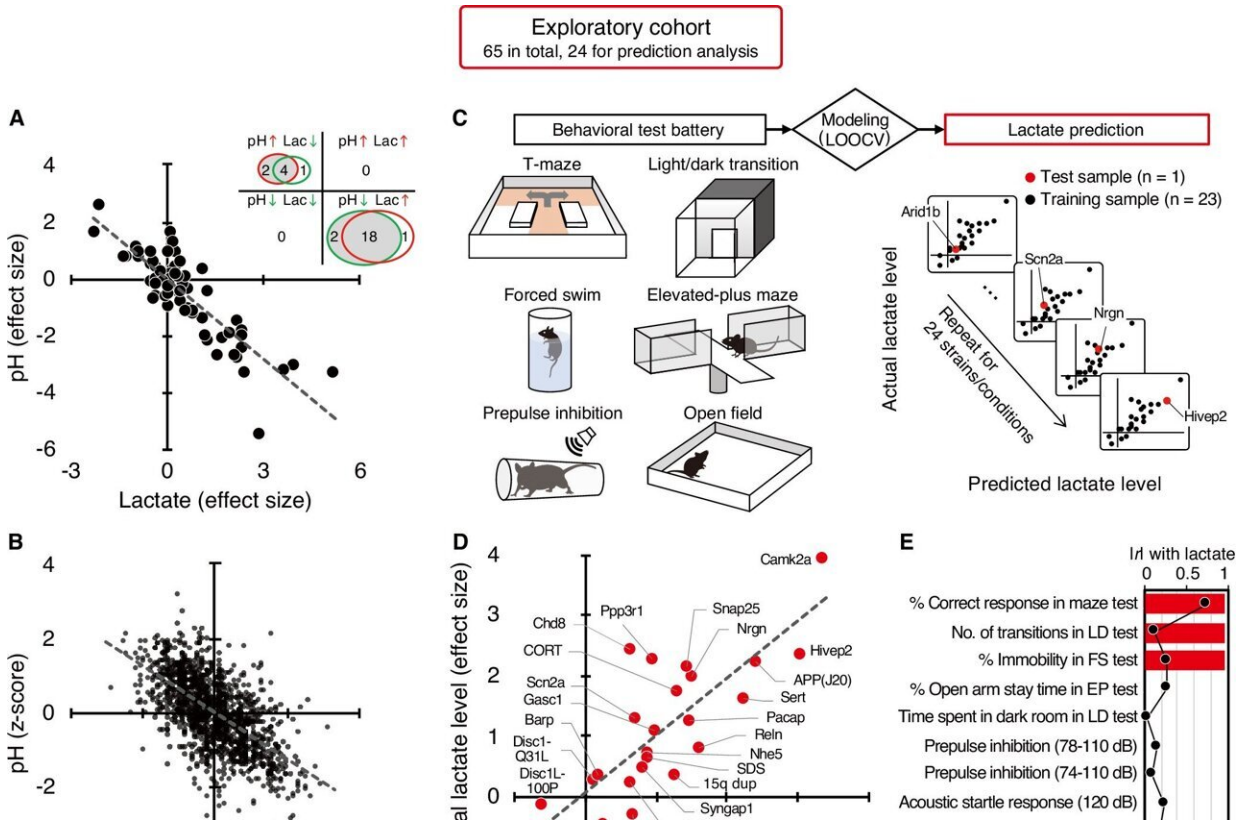
From autism to Alzheimer's: A large-scale animal study links brain pH changes to wide-ranging cognitive issues

March 26 2024



Increased brain lactate levels correlated with decreased pH are associated with poor working memory. Credit: eLife (2024). DOI: 10.7554/eLife.89376.3

A global collaborative research group comprising 131 researchers from 105 laboratories across seven countries has published a paper in *eLife*. The study identifies brain energy metabolism dysfunction leading to altered pH and lactate levels as common hallmarks in numerous animal models of neuropsychiatric and neurodegenerative disorders, such as intellectual disability, autism spectrum disorders, schizophrenia, bipolar disorder, depressive disorders, and Alzheimer's disease.

At the forefront of neuroscience research, the research group sheds light on altered energy metabolism as a key factor in various neuropsychiatric and neurodegenerative disorders. While considered controversial, an elevated lactate level and the resulting decrease in pH is now also proposed as a potential primary component of these diseases.

Unlike previous assumptions associating these changes with external factors like medication, the research group's previous findings suggest that they may be intrinsic to the disorders. This conclusion was drawn from five animal models of schizophrenia/developmental disorders, bipolar disorder, and autism, which are exempt from such confounding factors.

However, research on brain pH and lactate levels in animal models of other neuropsychiatric and neurological disorders has been limited. Until now, it was unclear whether such changes in the brain were a common phenomenon. Additionally, the relationship between alterations in brain pH and lactate levels and specific behavioral abnormalities had not been clearly established.

This study, encompassing 109 strains/conditions of mice, rats, and chicks, including animal models related to neuropsychiatric conditions, reveals that changes in brain pH and lactate levels are a common feature

in a diverse range of animal models of diseases, including schizophrenia/developmental disorders, bipolar disorder, autism, as well as models of depression, epilepsy, and Alzheimer's disease. This study's significant insights include:

1. Common Phenomenon Across Disorders: About 30% of the 109 types of animal models exhibited significant changes in brain pH and lactate levels, emphasizing the widespread occurrence of energy metabolism changes in the brain across various neuropsychiatric conditions.
2. Environmental Factors as a Cause: Models simulating depression through psychological stress, and those induced to develop diabetes or colitis, which have a high comorbidity risk for depression, showed decreased brain pH and increased lactate levels. Various acquired environmental factors could contribute to these changes.
3. Cognitive Impairment Link: A comprehensive analysis integrating behavioral test data revealed a predominant association between increased brain lactate levels and impaired working memory, illuminating an aspect of cognitive dysfunction.
4. Confirmation in Independent Cohort: These associations, particularly between higher brain lactate levels and poor working memory performance, were validated in an independent cohort of animal models, reinforcing the initial findings.
5. Autism Spectrum Complexity: Variable responses were noted in autism models, with some showing increased pH and decreased lactate levels, suggesting subpopulations within the autism spectrum with diverse metabolic patterns.

"This is the first and largest systematic study evaluating brain pH and lactate levels across a range of animal models for neuropsychiatric and neurodegenerative disorders. Our findings may lay the groundwork for

new approaches to develop the transdiagnostic characterization of different disorders involving cognitive impairment," states Dr. Hideo Hagihara, the study's lead author.

Professor Tsuyoshi Miyakawa, the corresponding author, explains, "This research could be a stepping stone towards identifying shared therapeutic targets in various neuropsychiatric disorders. Future studies will center on uncovering treatment strategies that are effective across diverse animal models with brain pH changes.

"This could significantly contribute to developing tailored treatments for patient subgroups characterized by specific alterations in brain energy metabolism."

In this paper, titled "Large-scale animal model study uncovers altered brain pH and lactate levels as a transdiagnostic endophenotype of neuropsychiatric disorders involving cognitive impairment," the mechanistic insights into the reduction in pH and the increase in lactate levels remain elusive. However, it is known that lactate production increases in response to neural hyperactivity to meet the energy demand, and the authors seem to think this might be the underlying reason.

More information: Hideo Hagihara et al, Large-scale animal model study uncovers altered brain pH and lactate levels as a transdiagnostic endophenotype of neuropsychiatric disorders involving cognitive impairment, *eLife* (2024). DOI: 10.7554/eLife.89376.3

Provided by Fujita Health University