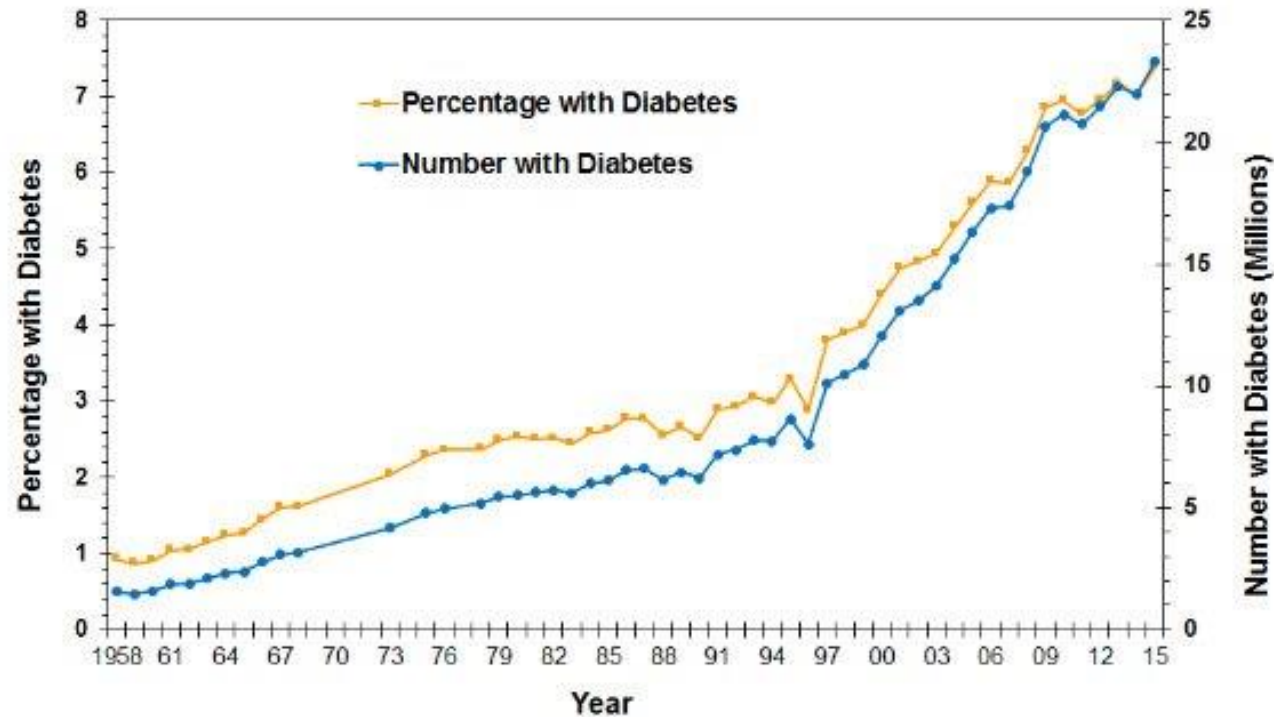


DR. IAIN CAMPBELL.
BASZUCKI BRAIN RESEARCH FELLOW IN METABOLIC PSYCHIATRY.
THE UNIVERSITY OF EDINBURGH.

From Neurotransmission to Neurometabolism: Bipolar Disorder and Epilepsy

Epidemic of Metabolic Syndrome and Diabetes

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015



CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/data>

The rise of insulin resistance. Pre-diabetes.

1980

108 Million worldwide with Diabetes
Prevalence in adults: 4.7%

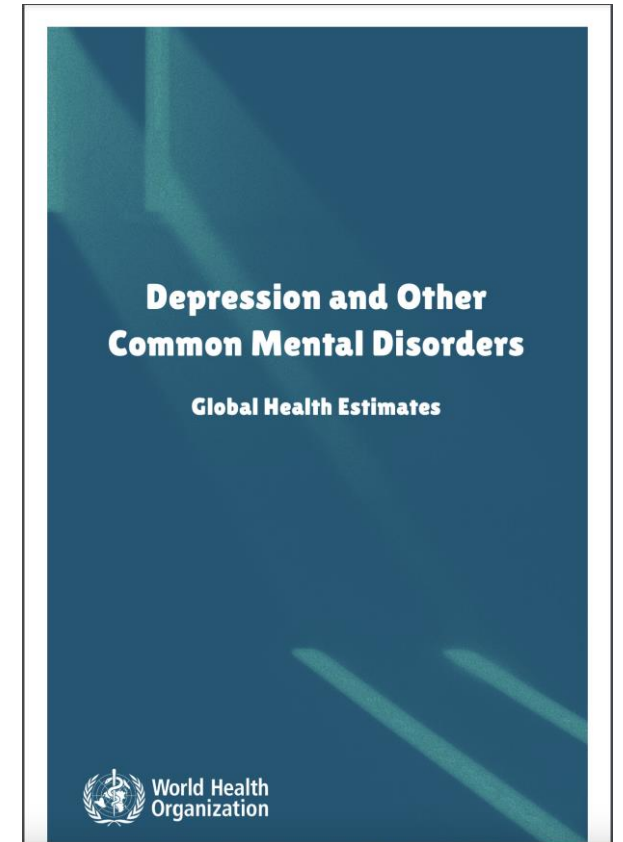
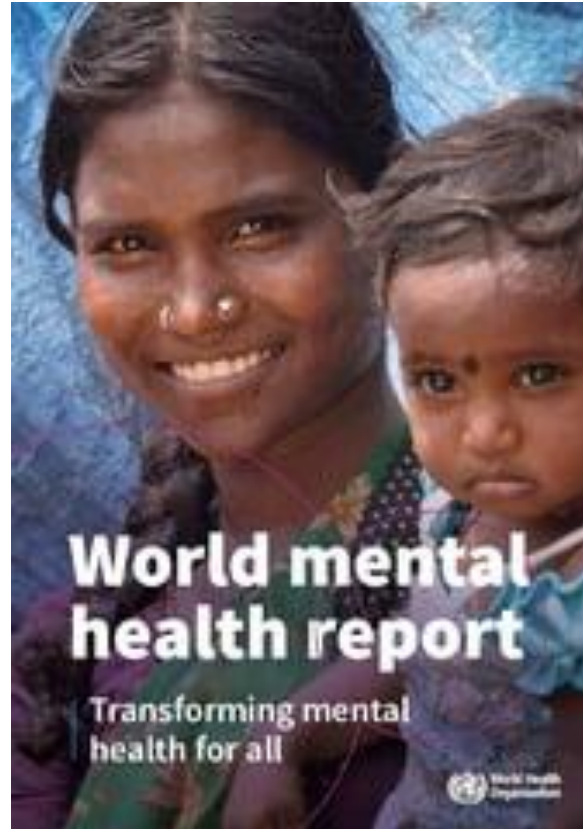
2014

422 Million worldwide with Diabetes
Prevalence in adults: 8.5%

<https://www.who.int/news-room/fact-sheets/detail/diabetes>

Twin Epidemics: Metabolic Health and Mental Health

- WHO estimate that nearly 1 billion people worldwide are now living with a mental disorder.
- Mental disorders are the leading cause of disability, causing 1 in 5 years lived with disability.
- People with severe mental health conditions die on average 10 to 20 years earlier than the general population, mostly due to preventable physical diseases.

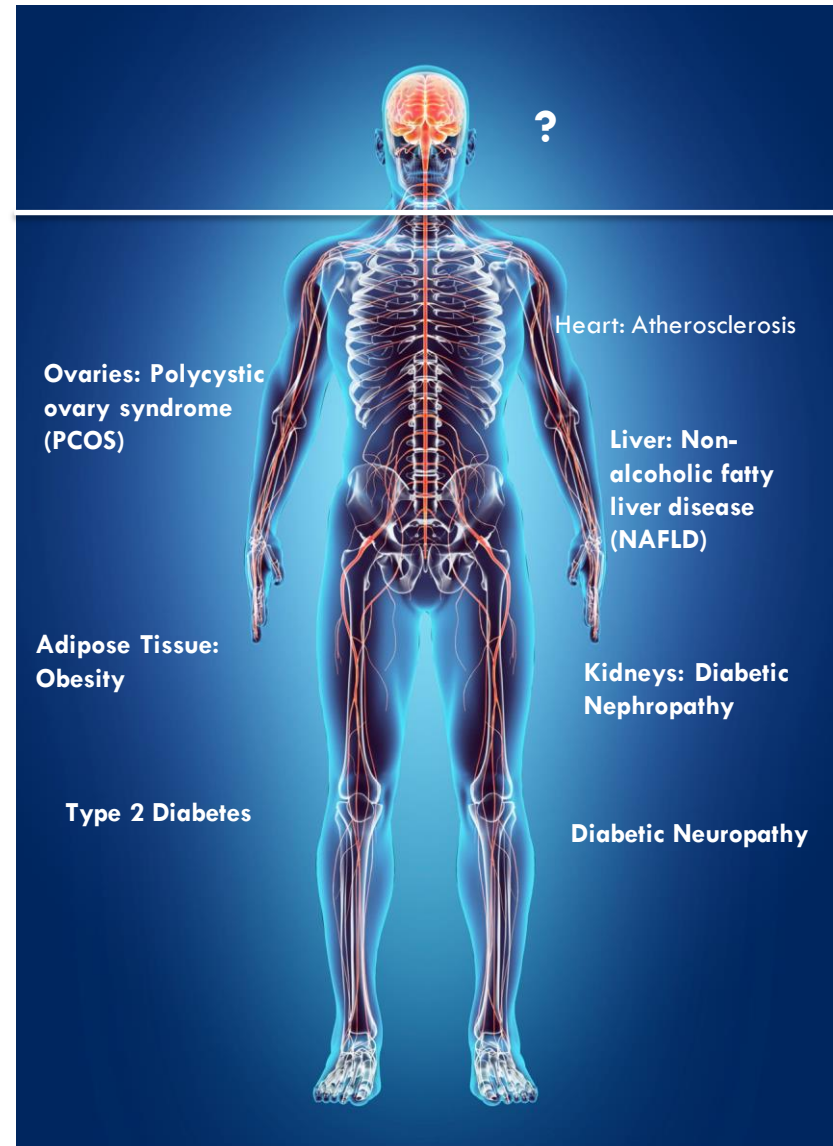


WHO World Mental Health Report 2019

WHO Depression and Other Common Mental Disorders 2017

Epidemic of Metabolic Syndrome and Diabetes

- Metabolic dysfunction and insulin resistance affects every major organ of the body.
- Why would the brain be isolated from this damage?



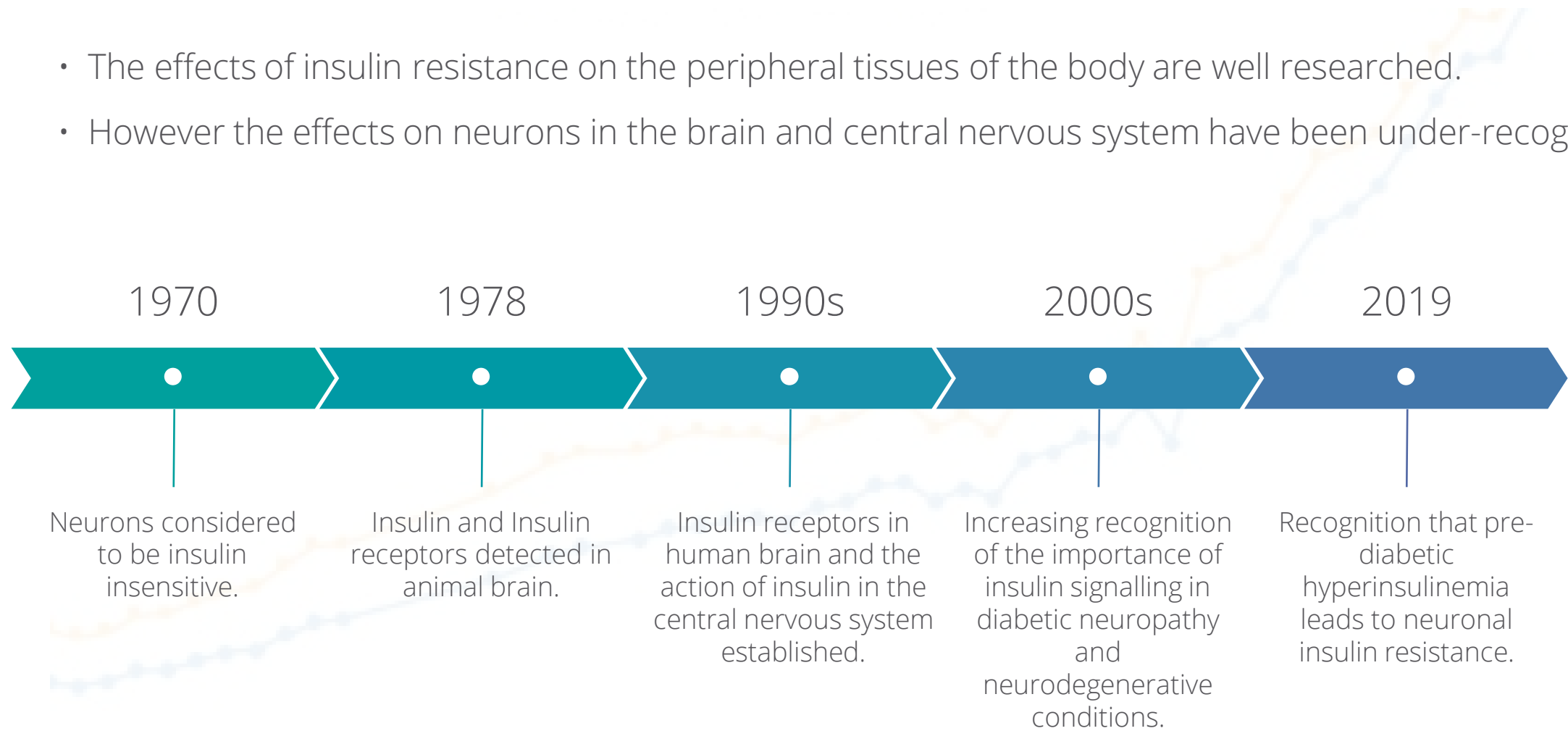
Energy in the Brain

- The brain is ~2% of human body weight.
- Yet it accounts for around 20% of the oxygen and therefore calories burned by the body.
- Highly sensitive to energy deficit caused by metabolic dysfunction.
- Bipolar disorder is one of the clearest examples of energy dysregulation in serious mental illness.

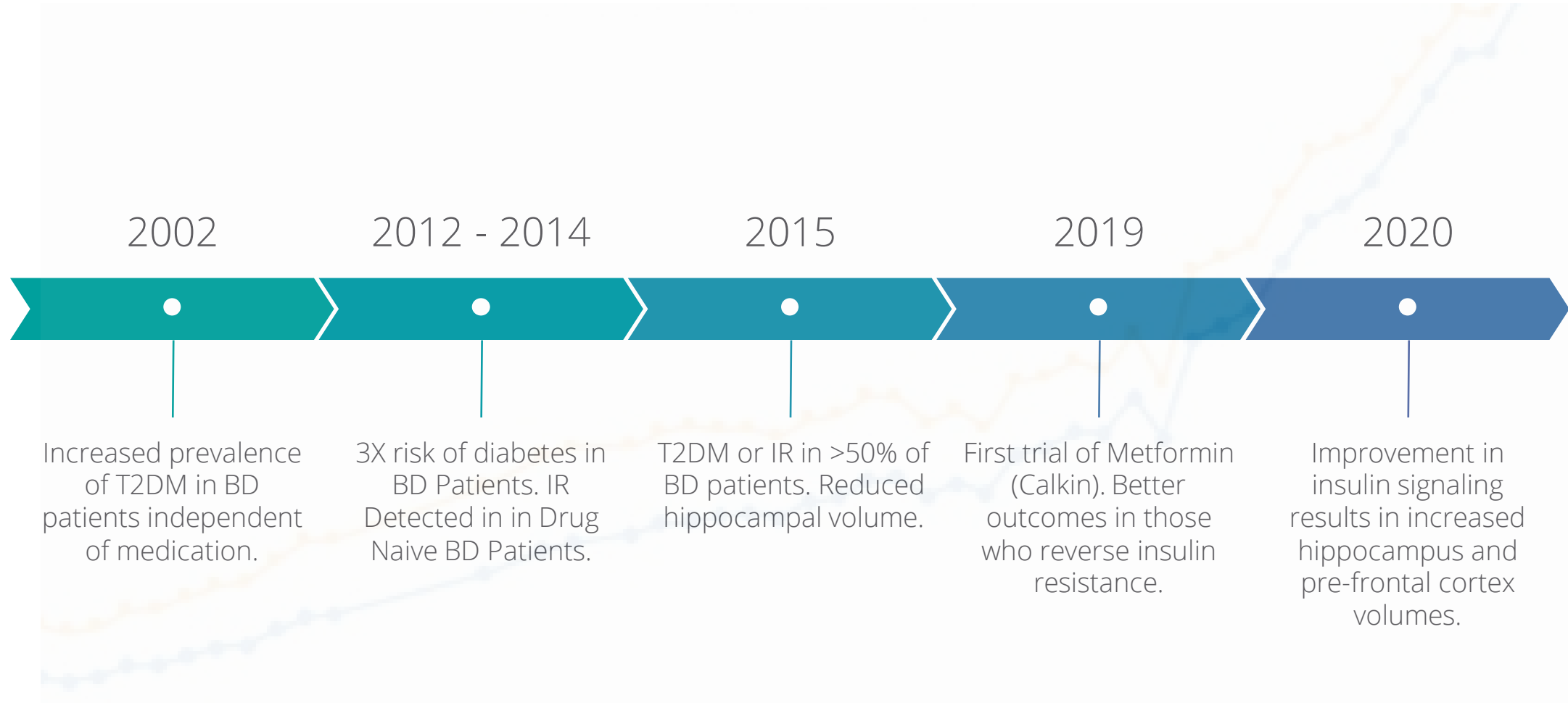


Research Timeline: Insulin Resistance in the Brain

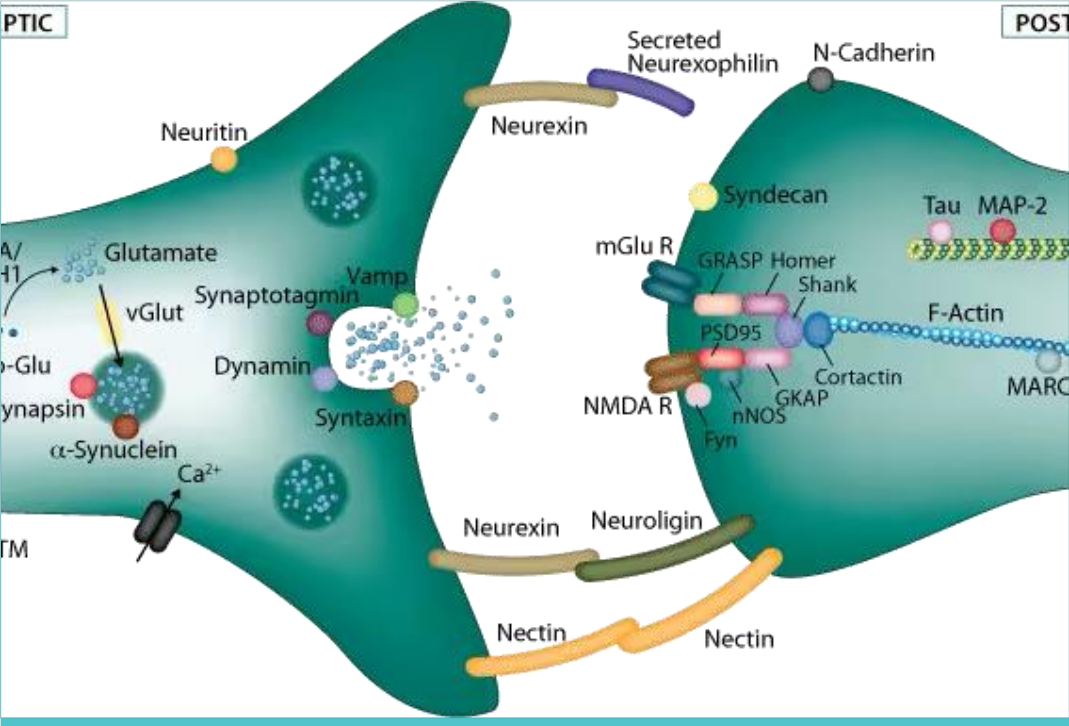
- The effects of insulin resistance on the peripheral tissues of the body are well researched.
- However the effects on neurons in the brain and central nervous system have been under-recognised.



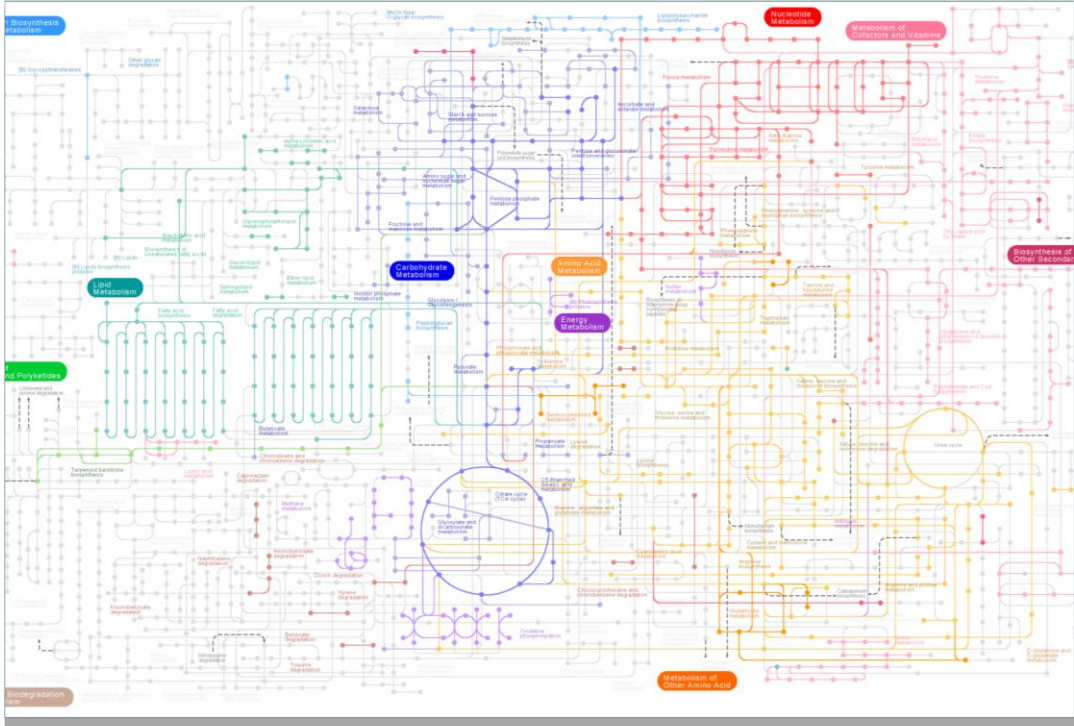
Research Timeline: Insulin Resistance in Bipolar Disorder



Neurotransmission to Neurometabolism



Neurotransmission



Neurometabolism

Neurotransmission & Neurometabolism

Little evidence that chemical imbalance causes depression, UCL scientists find

Researchers question use of antidepressants, prescribed to one in six UK adults



Neurotransmission

Systematic Review | [Open access](#) | [Published: 20 July 2022](#)

The serotonin theory of depression: a systematic umbrella review of the evidence

[Joanna Moncrieff](#) , [Ruth E. Cooper](#), [Tom Stockmann](#), [Simone Amendola](#), [Michael P. Hengartner](#) & [Mark A. Horowitz](#)

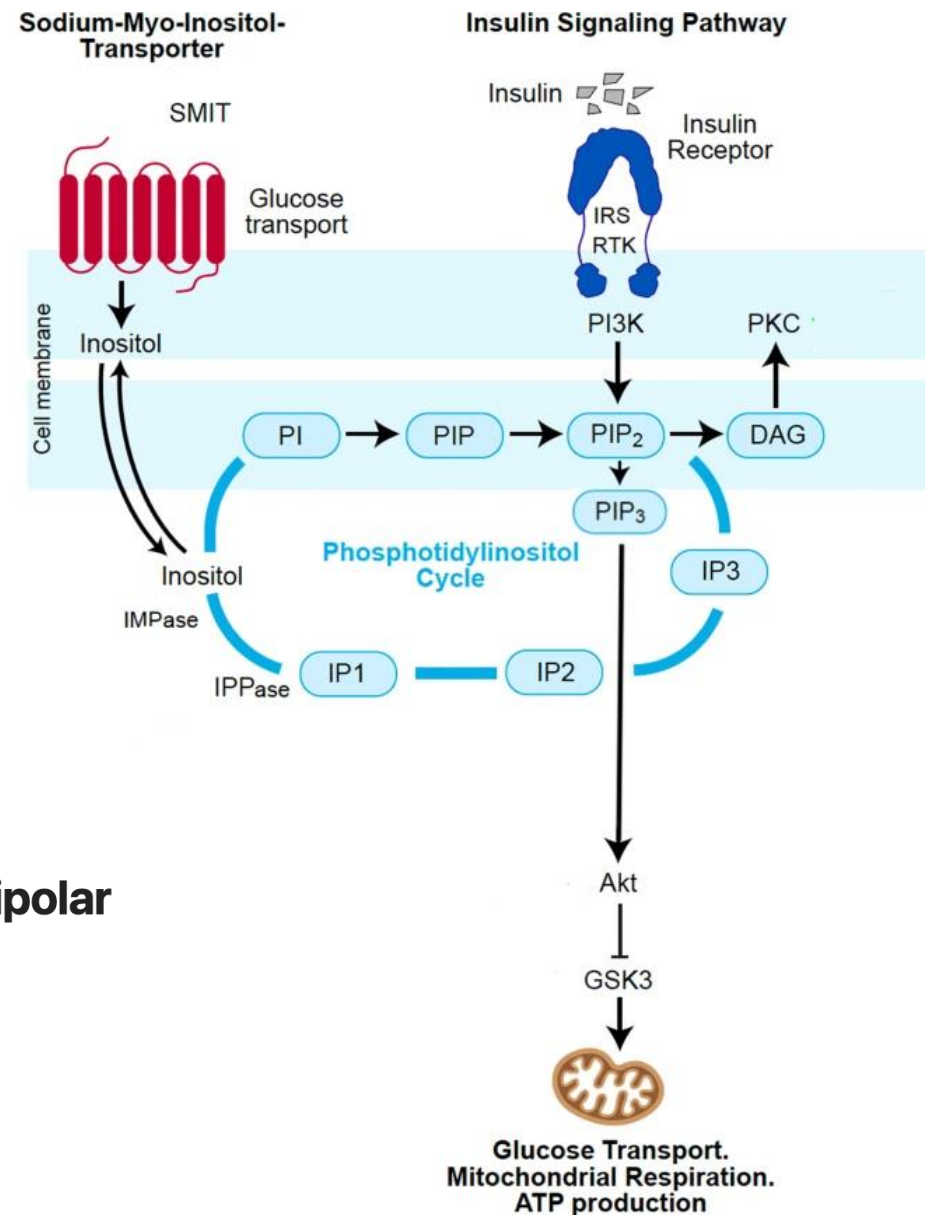
[Molecular Psychiatry](#) (2022) | [Cite this article](#)

1.12m Accesses | 150 Citations | 9175 Altmetric | [Metrics](#)

“This review suggests that the huge research effort based on the serotonin hypothesis has not produced convincing evidence of a biochemical basis to depression.”

HOW DOES METABOLIC DYSFUNCTION EXPRESS IN THE BRAIN?

- PI3K/AKT Insulin Signalling plays a significant role.
- Regulates brain energy through glucose metabolism and mitochondrial function.



Perspective | [Open access](#) | [Published: 29 August 2022](#)

Insulin signaling as a therapeutic mechanism of lithium in bipolar disorder

[Iain H. Campbell](#) , [Harry Campbell](#) & [Daniel J. Smith](#)

[Translational Psychiatry](#) **12**, Article number: 350 (2022) | [Cite this article](#)

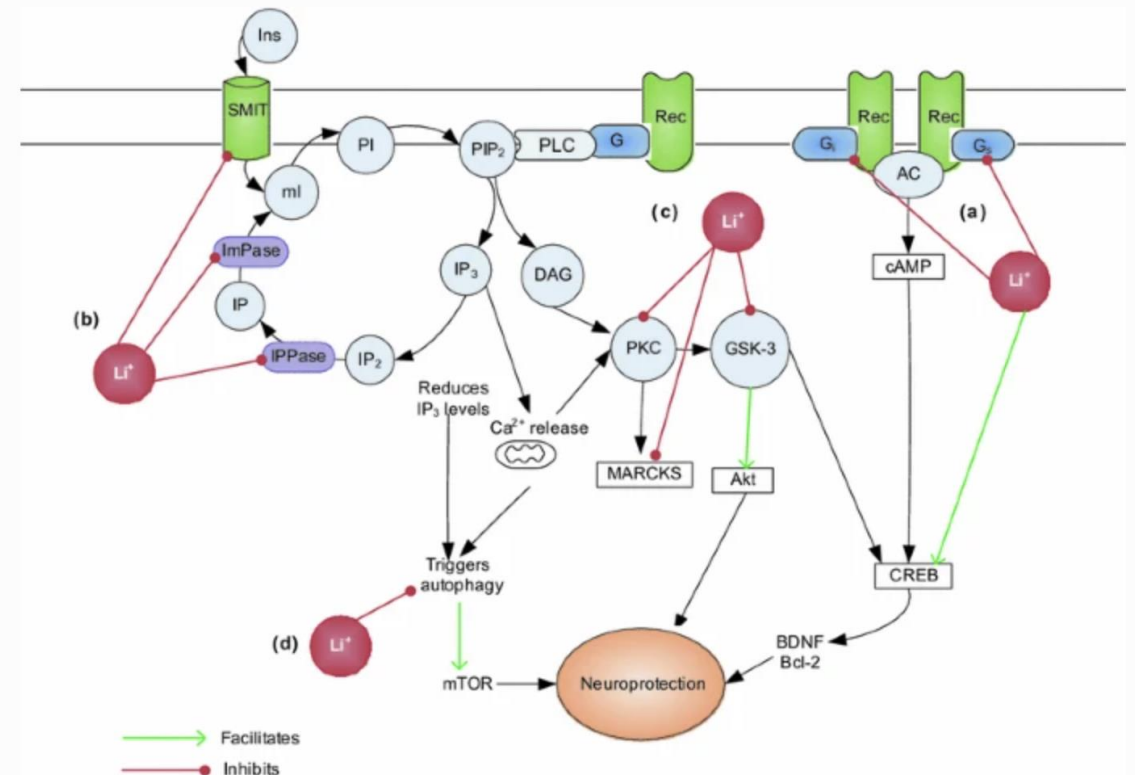
MECHANISMS OF ACTION OF LITHIUM FROM NEUROTRANSMISSION TO NEUROMETABOLISM

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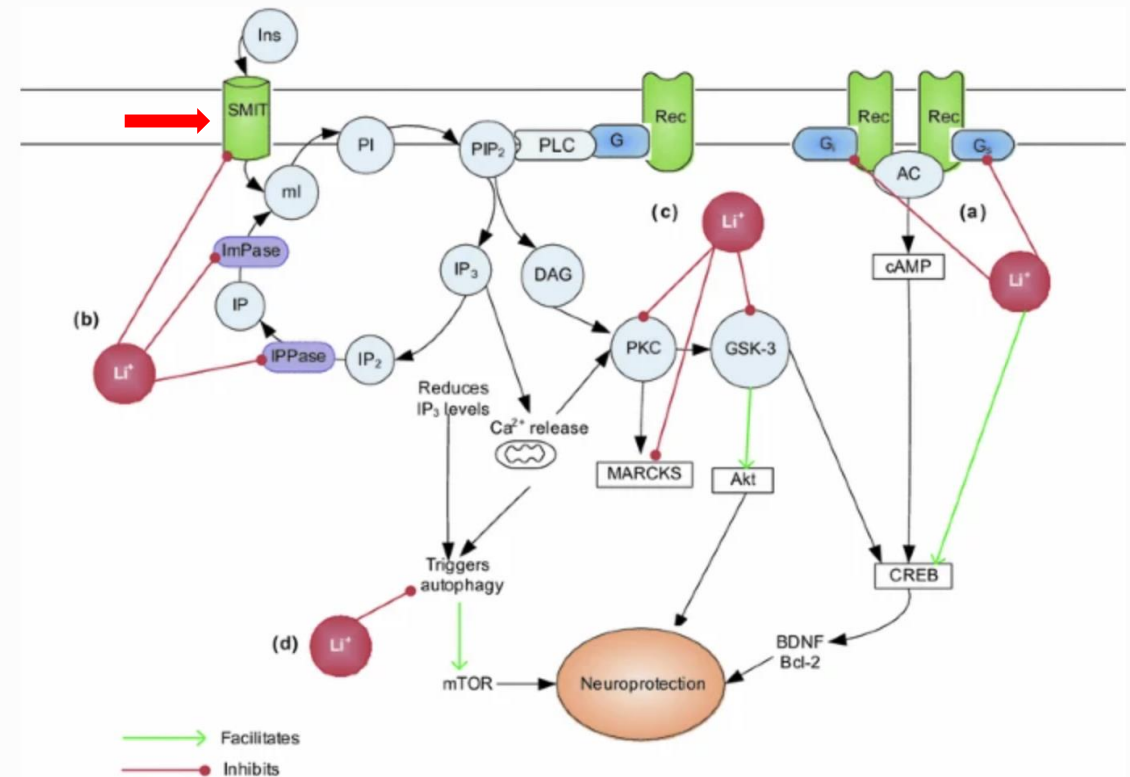
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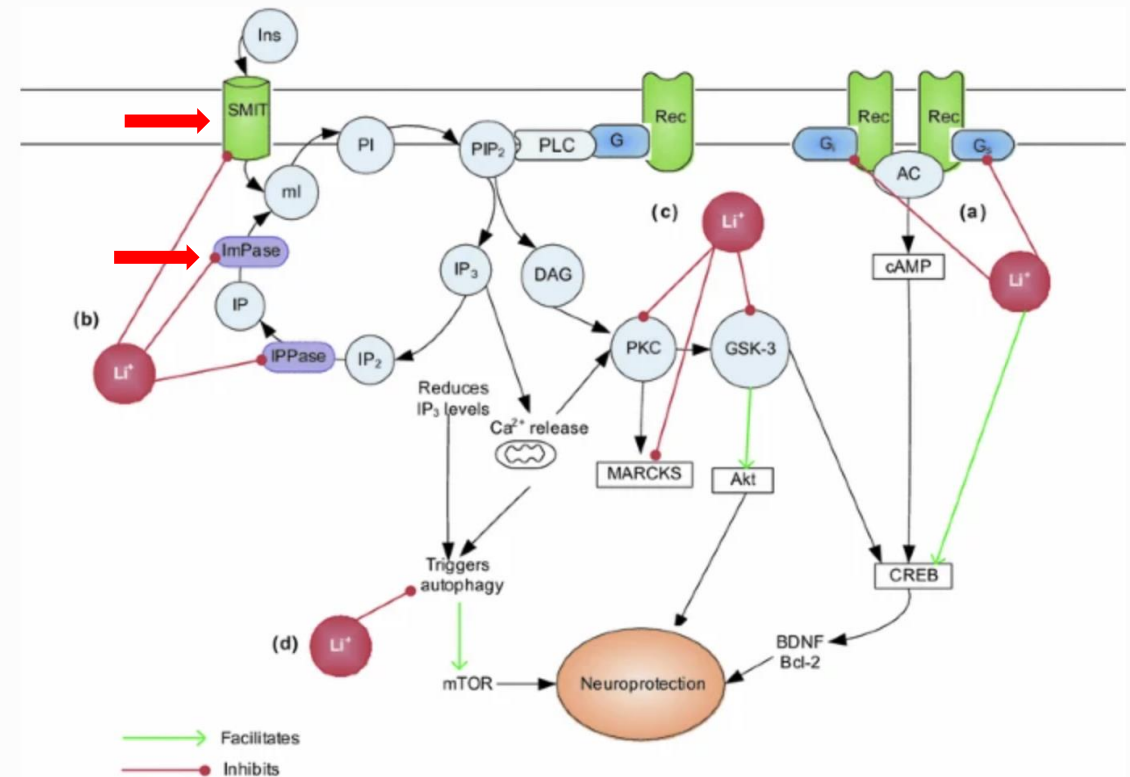
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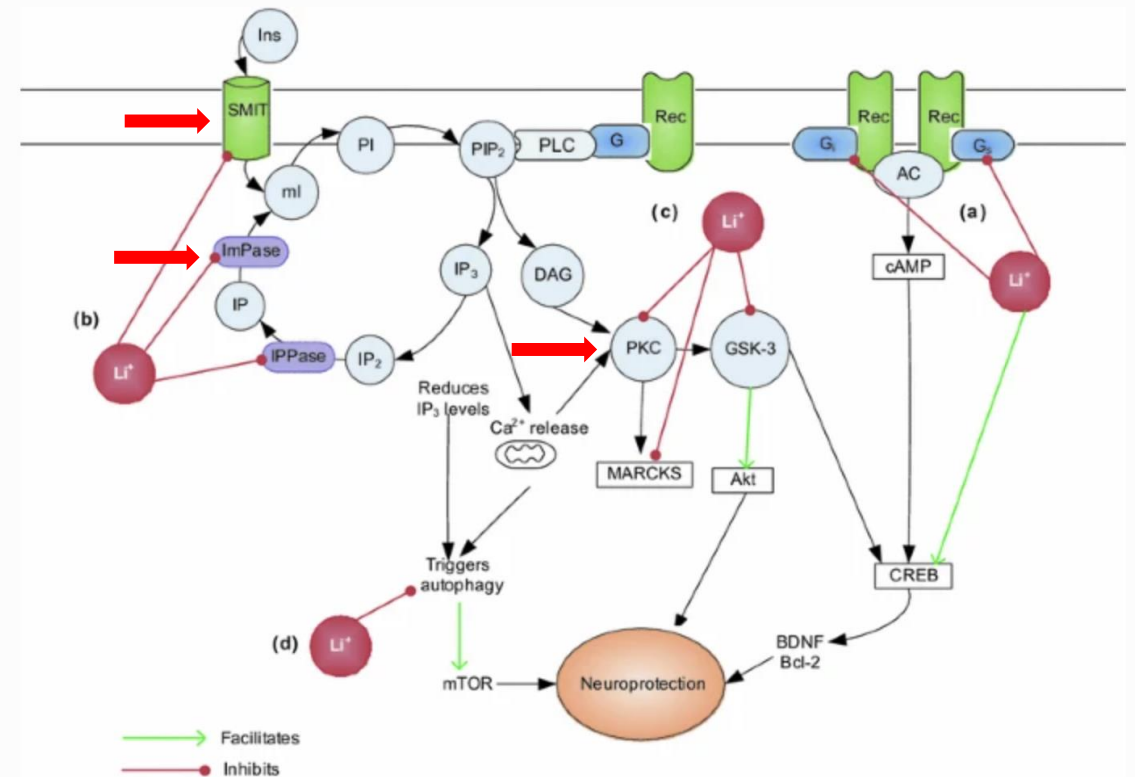
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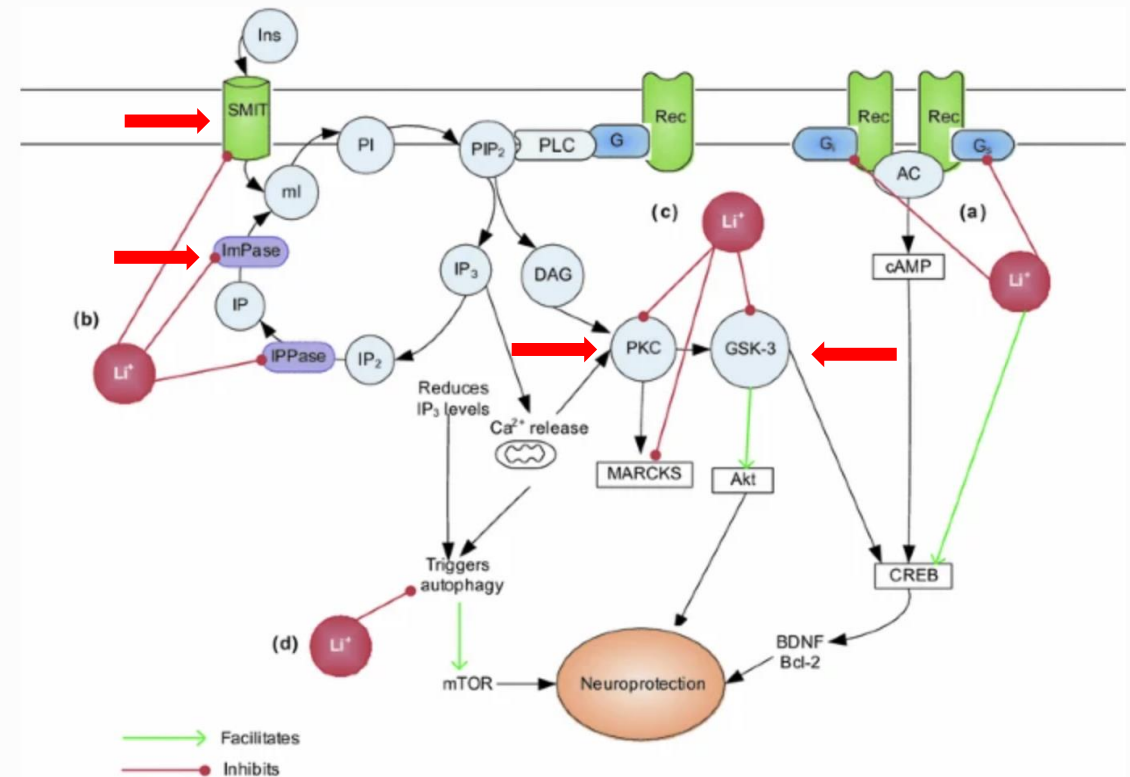
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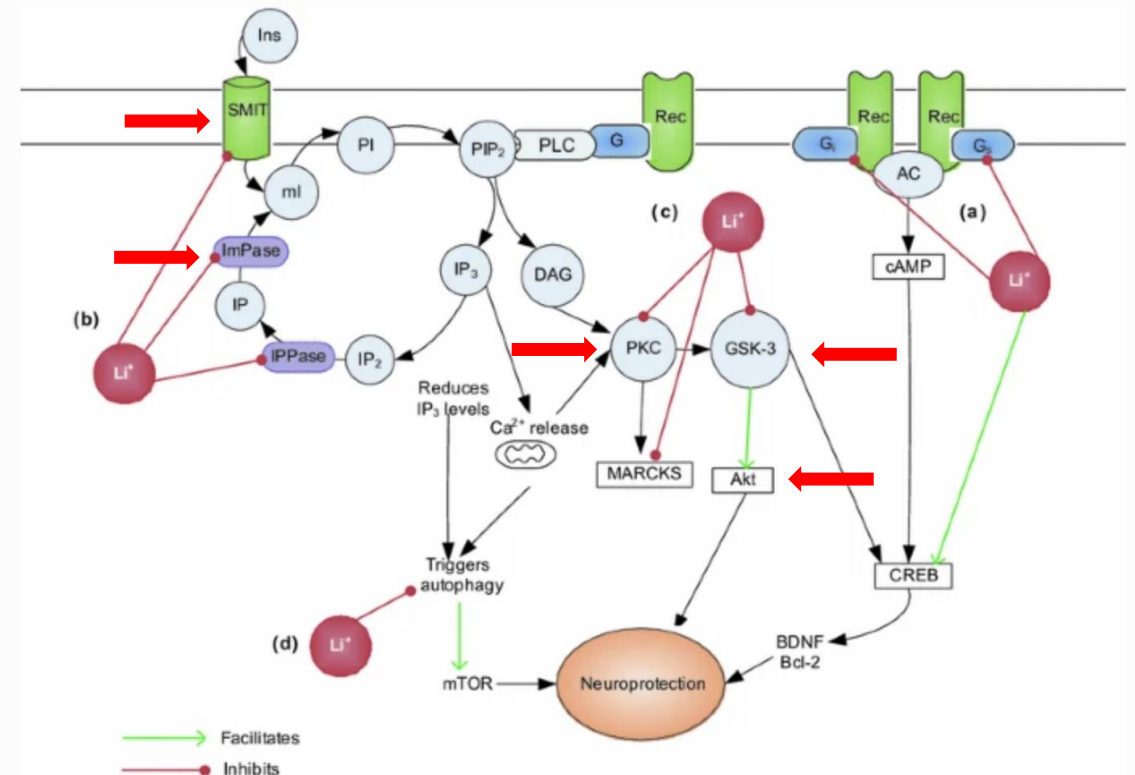
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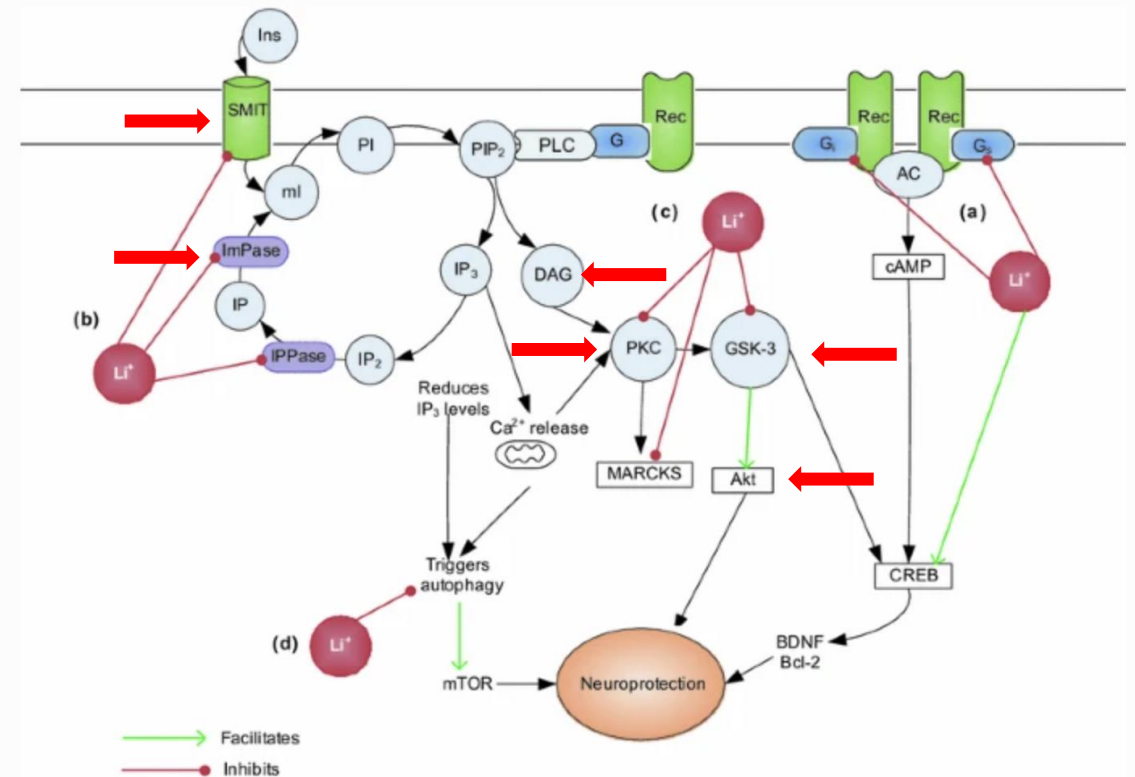
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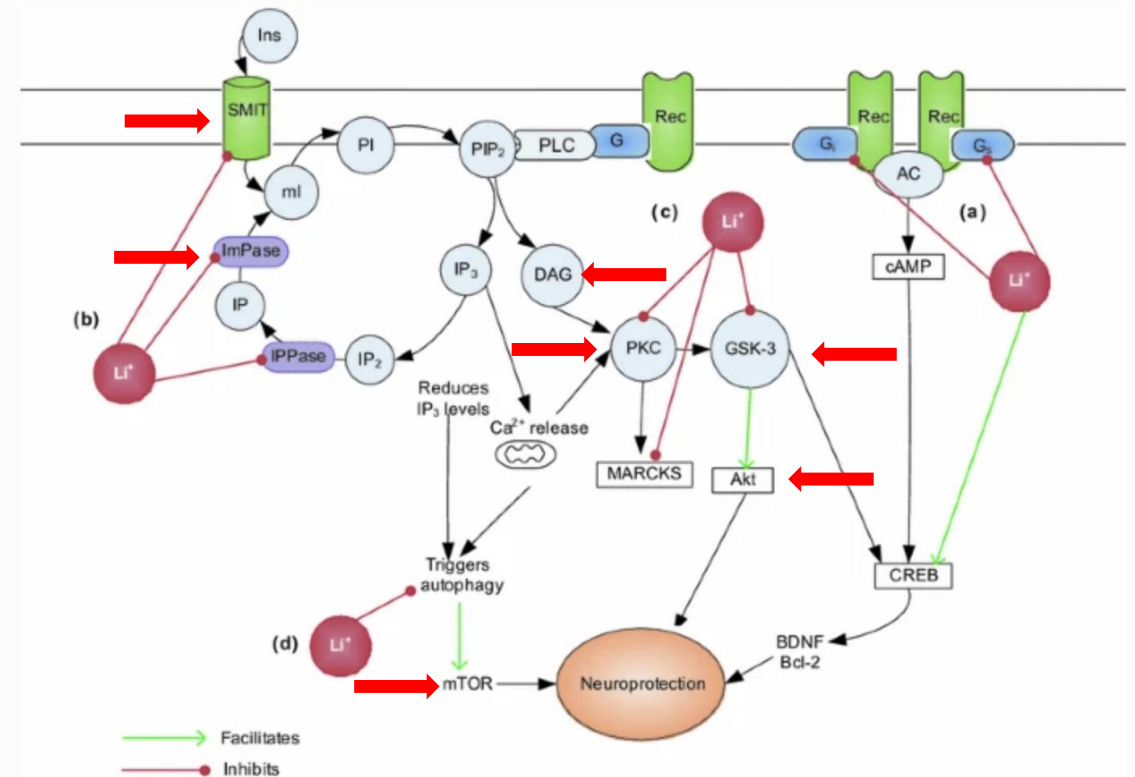
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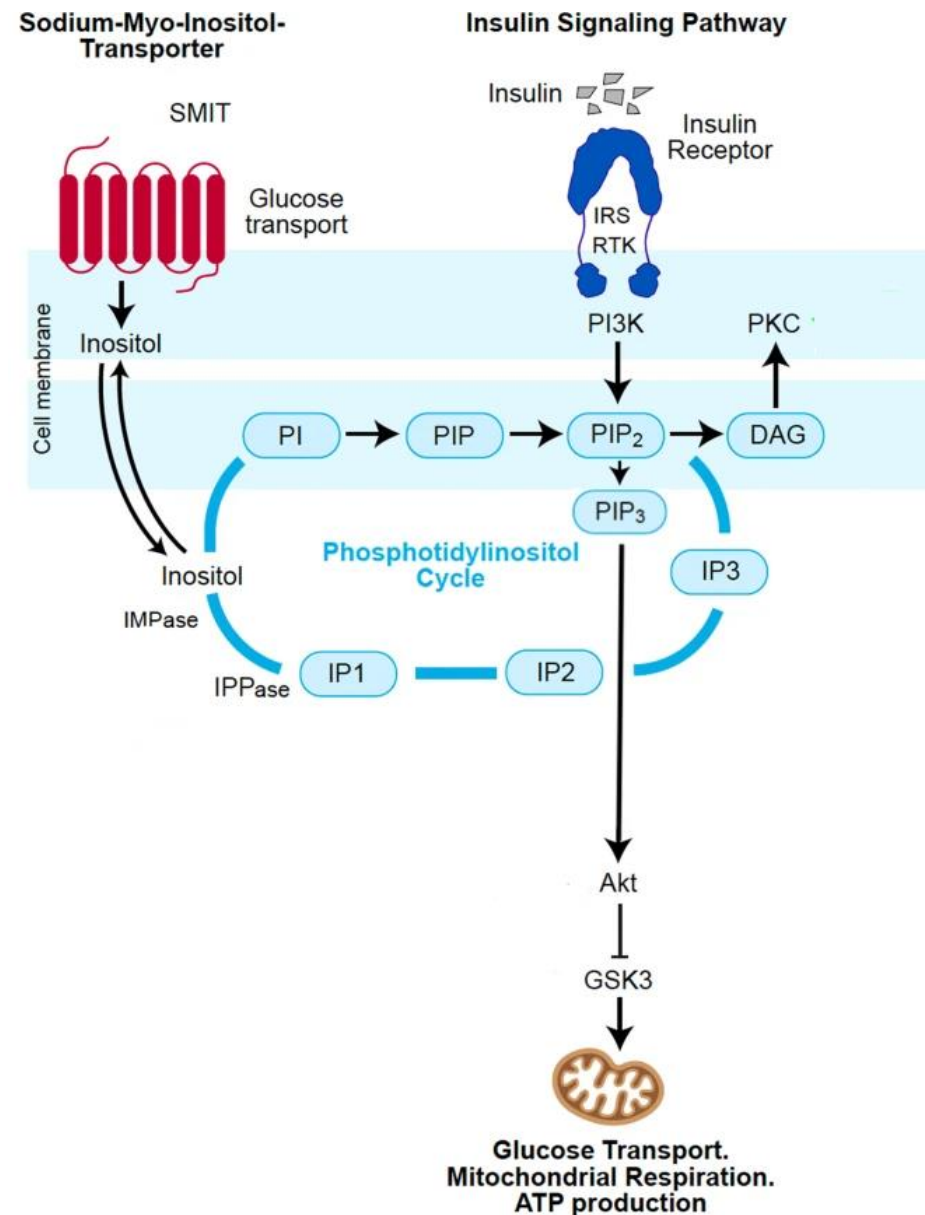
LITHIUM AND INSULIN SIGNALLING

Table 1 The actions of lithium on second messenger systems

Li ⁺ target	Role in cellular signalling	Change in BD	Action of Li ⁺
AC and cAMP	AC and cAMP are activated by monoaminergic transmission. This stimulates second messengers that consequently regulate neurotransmission [125]	Sensitivity of the system is altered resulting in modulation of excitatory neurotransmission [125]	Modulation of neurotransmission, by increasing basal levels of AC and cAMP such that large fluctuations that normally occur in response to monoaminergic stimulation are minimized [9, 126, 130]
SMIT	Responsible for regulation of inositol entry into the cell [134]	Upregulated in BD I [135]	Inhibits SMIT expression and activity, thereby limiting transport into the cell and contributes to depletion of intracellular inositol [135]
ImPase and IPPase	These are rate-limiting enzymes in the PI cycle involved in changing IP ₂ to IP and IP to mI, respectively [125]	↑ in both mania and depression [102]	Direct inhibition of ImPase and IPPase. Thus, recycling to restore intracellular inositol is limited causing depletion [136]
PKC	Modulates pre- and post-synaptic transmission [132, 144]	↑ in mania [144, 145]	Inhibits PKC thereby reducing excitatory neurotransmission [132, 138, 144]
MARCKS	Downstream target of PKC that is responsible for release of neurotransmitters [132]	↑ in mania [146, 148]	Inhibits MARCKS directly [148] and indirectly via its action on PKC [132, 138, 147]
BDNF and Bcl-2	Neuroprotective proteins that are activated by CREB, which is a downstream target of AC and cAMP [9]	↓ in BD [181, 188]	Increases BDNF [182] and Bcl-2 [187–189] levels as a consequence of CREB activation through the actions of lithium on cAMP
GSK-3	Regulation of glycogen synthesis, gene transcription, synaptic plasticity and cell structure and resilience [131, 132]	Dysregulation [192] ^a	Inhibits GSK directly [193], which then activates the Akt neuroprotective pathway [195]

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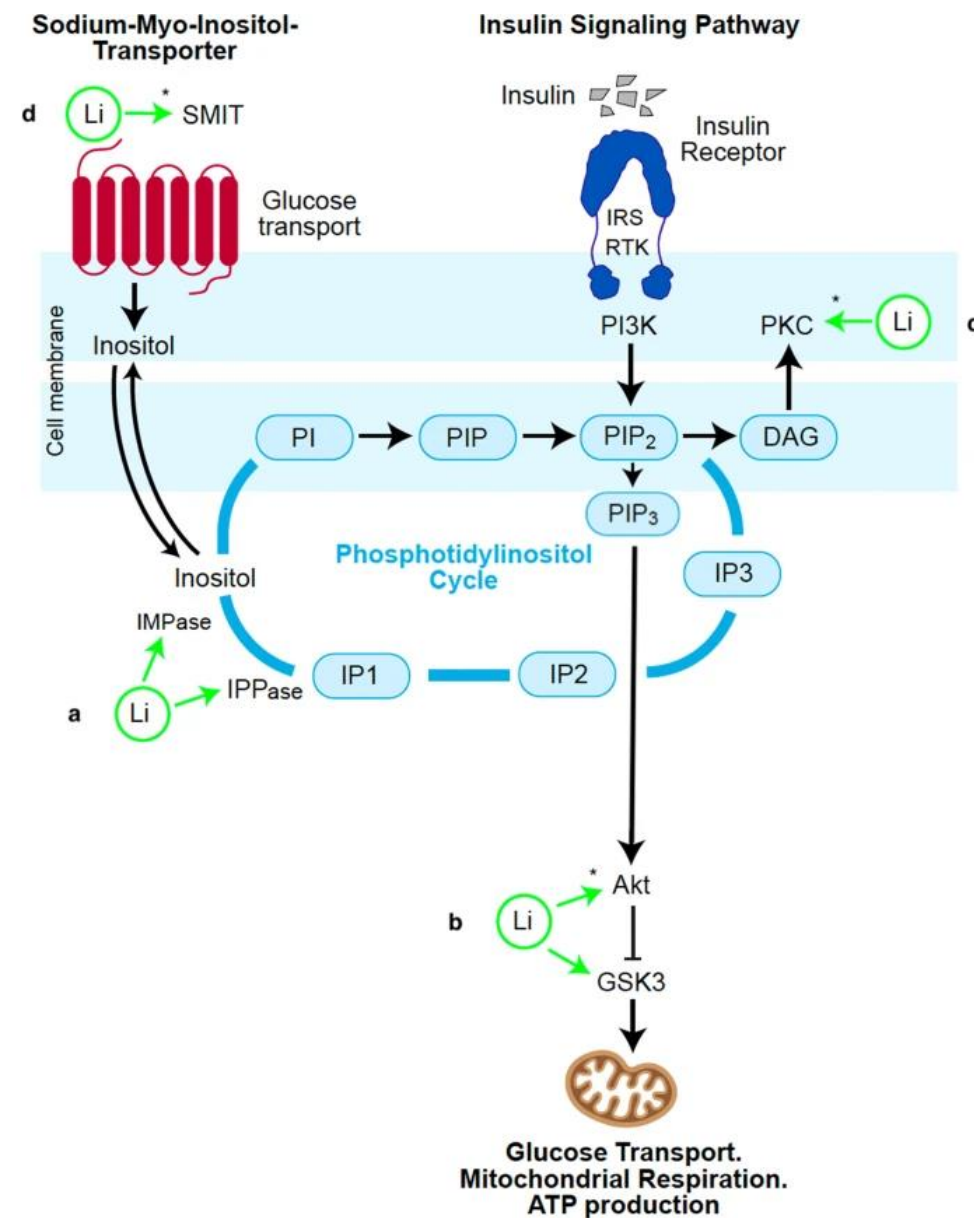
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WHAT IS INSULIN RESISTANCE IN THE BRAIN?

Perspective | [Open access](#) | [Published: 29 August 2022](#)

Insulin signaling as a therapeutic mechanism of lithium in bipolar disorder

[Iain H. Campbell](#) , [Harry Campbell](#) & [Daniel J. Smith](#)

[Translational Psychiatry](#) **12**, Article number: 350 (2022) | [Cite this article](#)

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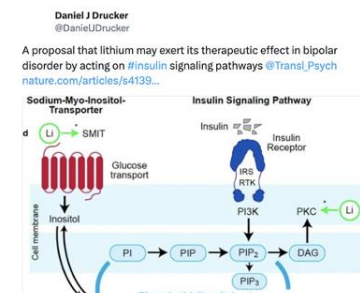
Molecular signatures of hyperexcitability and lithium responsiveness in bipolar disorder patient neurons provide alternative therapeutic strategies

Anouar Khayachi, Malak Abuzgaya, Yumin Liu, Chuan Jiao, Kurt Dejgaard, Lenka Schorova, Anusha Kamesh, Qin He, Yuting Cousineau, Alessia Pietrantonio, Nargess Farhangdoost, Charles-Etienne Castonguay, Boris Chaumette, Martin Alda, Guy A. Rouleau, Austen J. Milnerwood

doi: <https://doi.org/10.1101/2023.07.21.550088>

This article is a preprint and has not been certified by peer review [what does this mean?].

“We found the therapeutic effect of Lithium in Bipolar Disorder Lithium Responsive patients was associated with Akt signalling and confirmed that an Akt activator mimics Lithium.”



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TAKEAWAYS

- Metabolic dysfunction (insulin resistance, type 2 diabetes...) is highly prevalent in people with serious mental illness (SMI).
- It is increasingly apparent that metabolic dysfunction in the brain plays a significant, if not primary role in causing SMI.
- People with SMI have 2-3 X risk of cardiovascular disease and live 10 years less than people without SMI.
- Many of the existing treatments for serious mental illness further compromise metabolic health.
- Metabolic treatment strategies should therefore receive greater prioritisation in research and care to treat both physical comorbidities and mental health.

Bipolar Disorder and Epilepsy

Shared Mechanisms and Medications

Anti-seizure Medications

Carbamezapine, valproate, lamotrigine.

Episodic Occurrence

Heightened activity in the brain.

Increased Lactate

Indicating altered glucose metabolism.



Ketogenic Diet

Metabolic therapy. 13 RCTs in Epilepsy. >100 years of clinical use. Pilot studies in bipolar disorder.

Co-morbidity

Around 50 - 60% of people with epilepsy experience psychiatric symptoms.

Altered Glutamate/GABA

Excitatory/inhibitory neurotransmission.

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Systematic Review: Brain Imaging Biomarkers in Bipolar Disorder

- Systematic review indicates that brain glutamate level is consistently increased in BD.
(Chabert et al., 2022)
- Reduction in glutamate, glutamine, and Glx (glutamate+glutamine) in BD patients is considered a marker of response to pharmacological treatment
(Dong et al., 2021; Friedman et al., 2009; Frye et al., 2007; Mansur et al., 2021; Strawn et al., 2012; Yoon et al., 2009; but see Brennan et al., 2010; Godlewska et al., 2019; Machado-Vieira et al., 2015)
- And other therapies such as light therapy
(Benedetti et al., 2009; Melloni et al., 2022)

- Patients were scanned using 3 Tesla MRS to measure brain metabolite concentrations before and after the KD intervention.
- The Point Resolved Spectroscopy (PRESS) technique was used to measure from a single voxel in each region of interest.

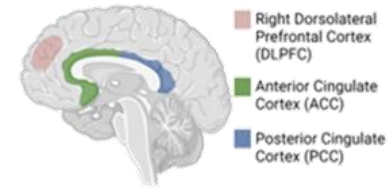
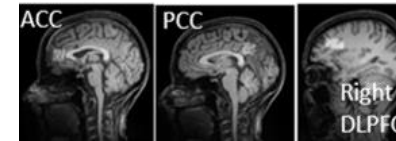
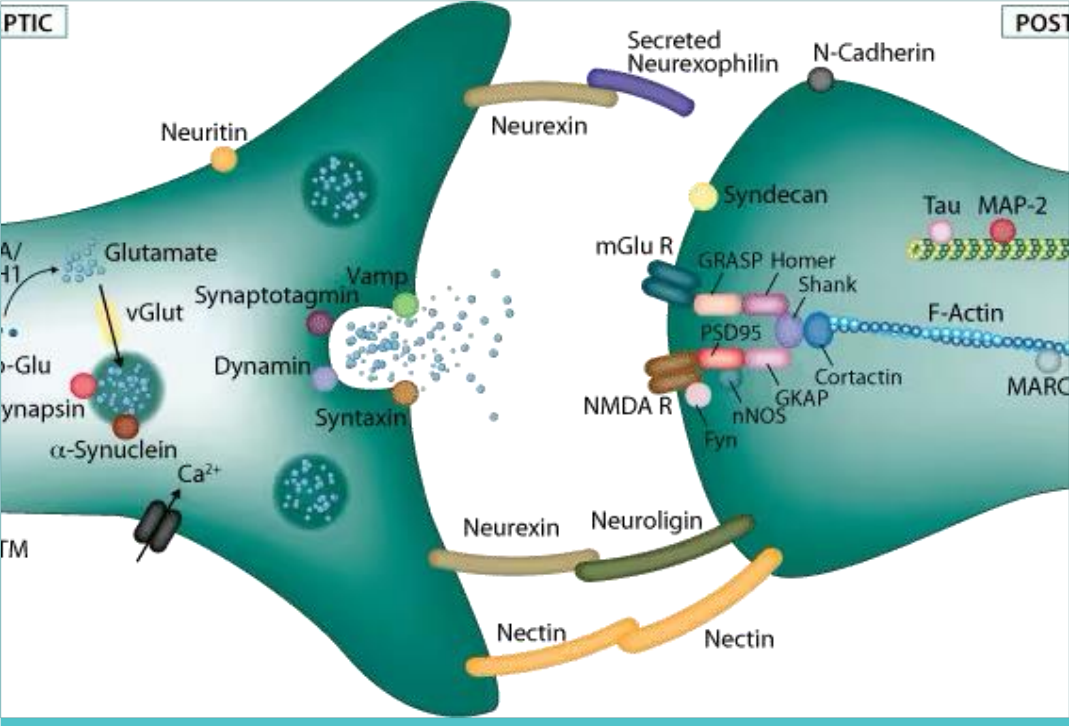


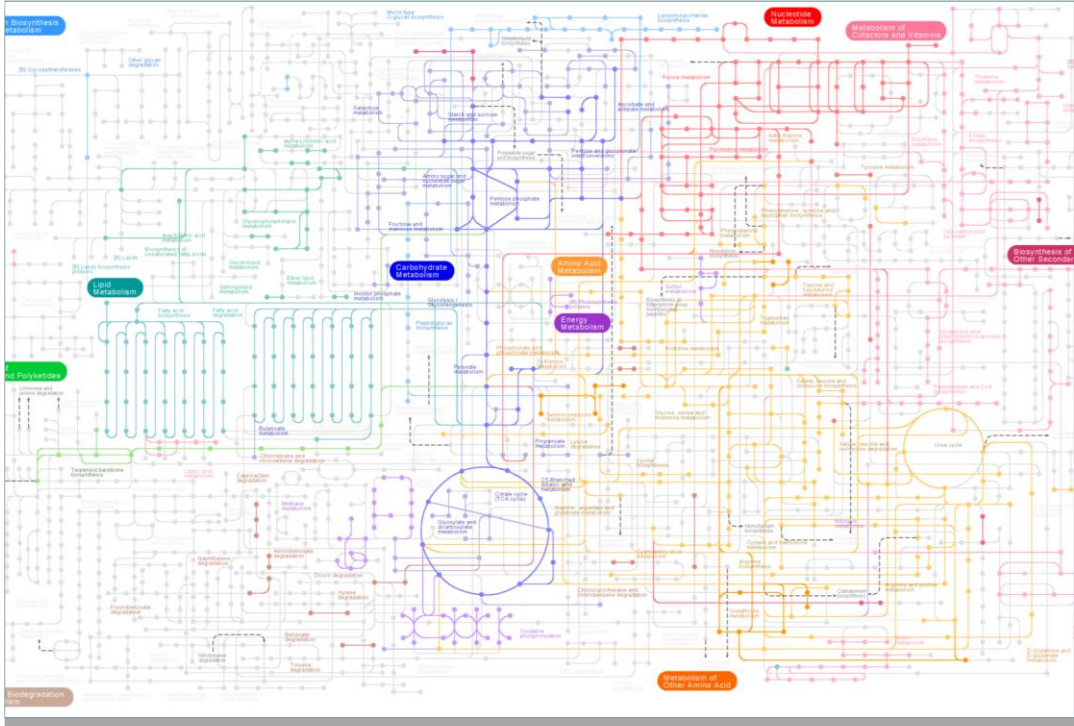
Fig 3. Brain areas implicated in the pathophysiology of bipolar disorder in previous neuroimaging studies were selected as regions of interest.²



Neurotransmission to Neurometabolism



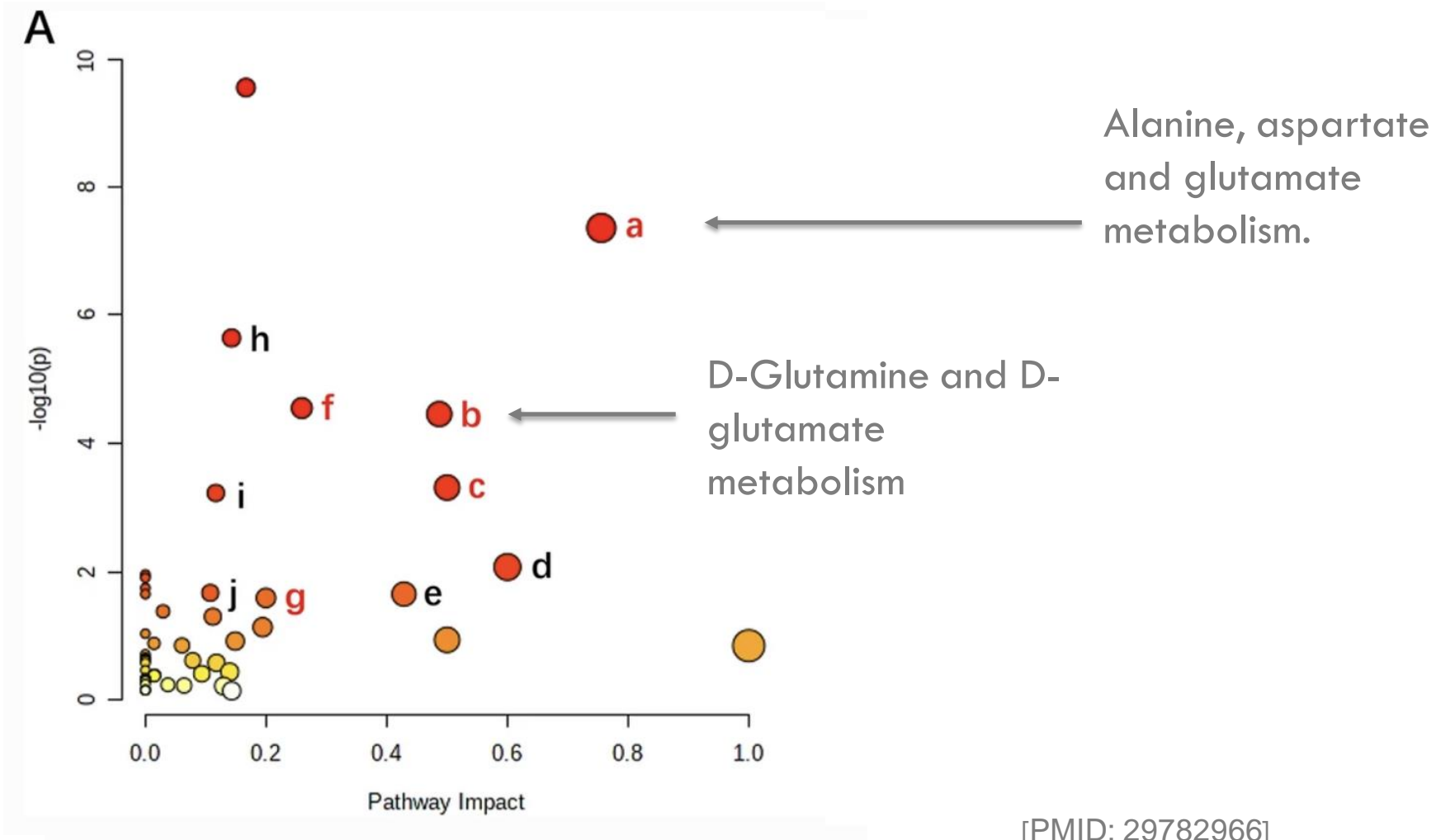
Neurotransmission



Neurometabolism

Review: Epilepsy Blood Biomarkers

“Changes in Glu, lactate and citrate are most common in the serum of people with epilepsy.”



[PMID: [29782966](#)]

Review: Epilepsy Blood Biomarkers

- Ketosis appears to downregulate glutamate metabolism in favour of GABA, promoting a reduced excitatory state in the brain.
- It has been suggested that this is an important mechanism of action in seizure reduction.
- Could this also explain some of the mood stabilising effects of a ketogenic diet?

> [Neuropsychopharmacology](#). 2023 Apr;48(5):797-805. doi: 10.1038/s41386-022-01364-8. Epub 2022 Aug 22.

Acute administration of ketone beta-hydroxybutyrate downregulates 7T proton magnetic resonance spectroscopy-derived levels of anterior and posterior cingulate GABA and glutamate in healthy adults

[Antoine Hone-Blanchet](#)¹, [Botond Antal](#)^{1 2}, [Liam McMahon](#)², [Andrew Lithen](#)², [Nathan A Smith](#)^{3 4}, [Steven Stufflebeam](#)¹, [Yi-Fen Yen](#)¹, [Alexander Lin](#)¹, [Bruce G Jenkins](#)¹, [Lilianne R Mujica-Parodi](#)^{1 2 5 6}, [Eva-Maria Ratai](#)⁷

Neuronal–glial interactions in rats fed a ketogenic diet

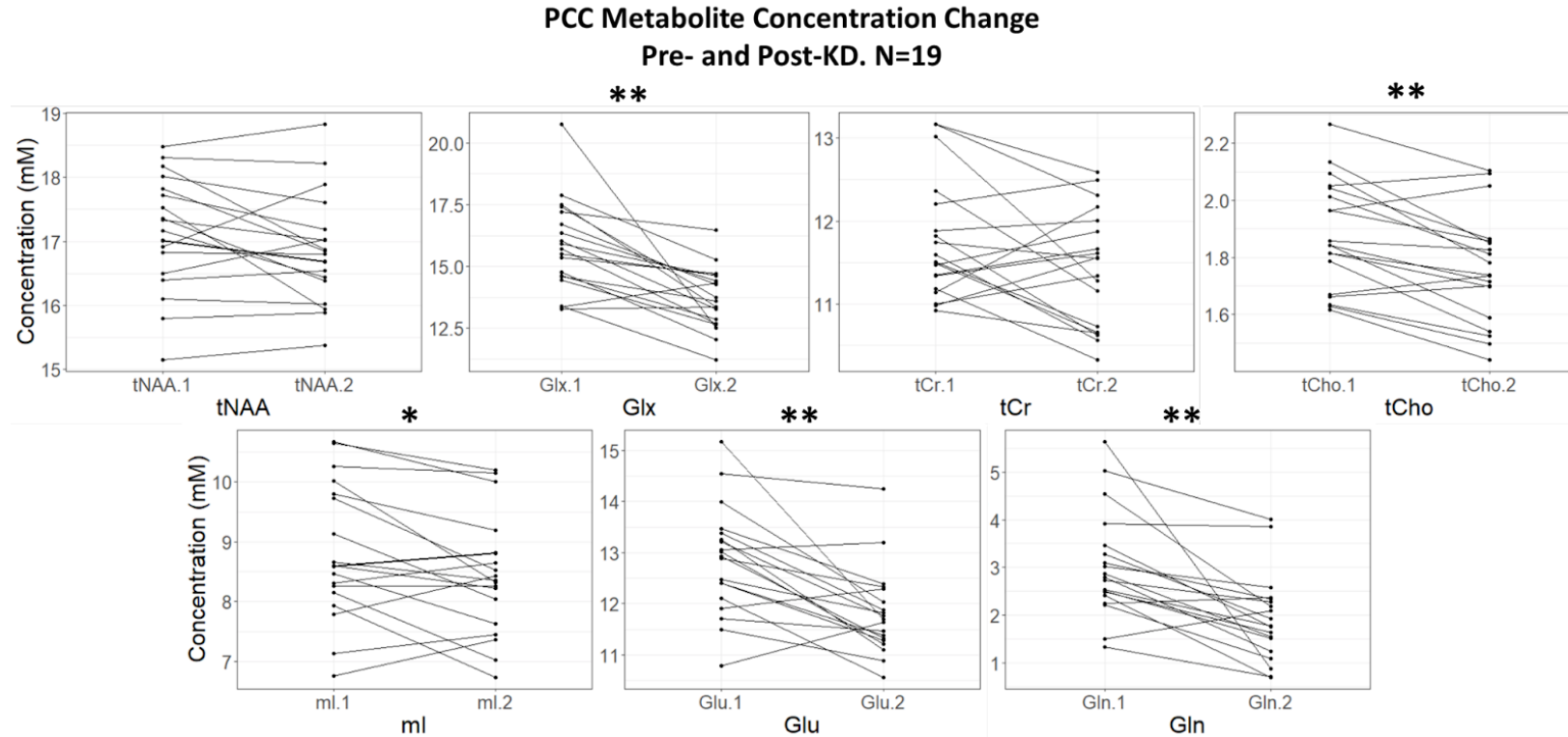
[Torun Margareta Melø](#)^a  , [Astrid Nehlig](#)^b, [Ursula Sonnewald](#)^a

[Show more](#) 

Ketosis and brain handling of glutamate, glutamine, and GABA

[Marc Yudkoff](#), [Yevgeny Daikhin](#), [Oksana Horyn](#), [Ilana Nissim](#), [Itzhak Nissim](#)

Magnetic Resonance Spectroscopy (MRS) Edinburgh Pilot Study of a Ketogenic Diet For Bipolar Disorder



- Glx decreased from baseline by 9.22% in the ACC ($p < 0.02$)
- Glx decreased from baseline by 13.13% in the PCC ($p < 0.001$)

Glutamate as a Metabolic Fuel Source

- Research in bipolar disorder has primarily focused on the role of glutamate as an excitatory neurotransmitter.
- However, the role of glutamate as a metabolic substrate was an original focus of Hans Krebs research throughout the 1960s.
- Focus of research shifted to its function as an excitatory neurotransmitter later in 1980s.

Biochem. J. (1963) **88**, 566

The Metabolism of Glutamate in Homogenates and Slices of Brain Cortex

BY R. J. HASLAM* AND H. A. KREBS

Medical Research Council Unit for Research in Cell Metabolism, Department of Biochemistry, University of Oxford

(Received 18 March 1963)

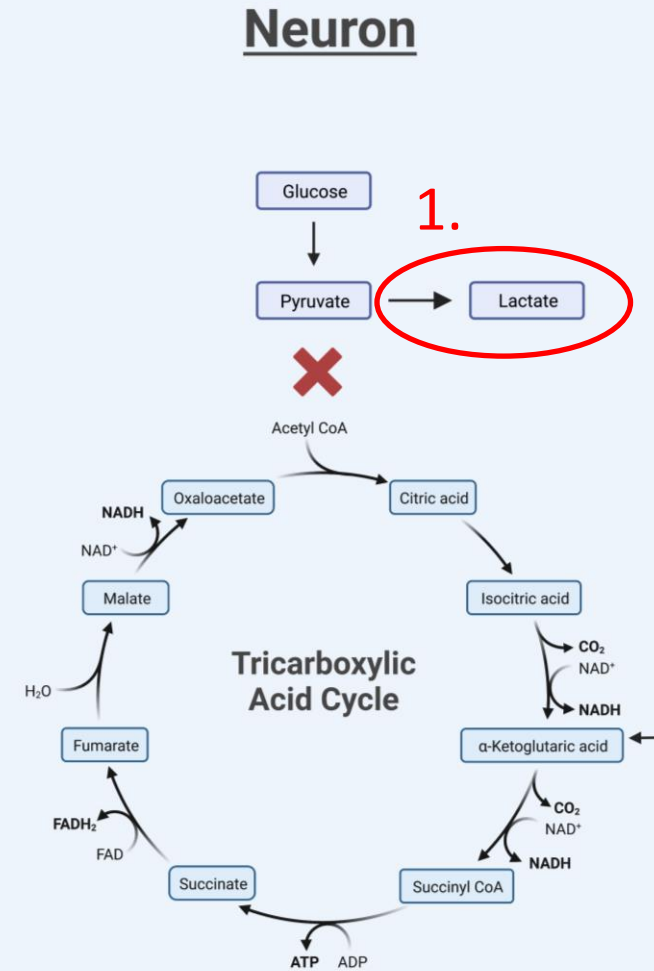
Glutamate is a highly active metabolite in the cerebral cortex. It can be converted into α -oxoglutarate by transamination or dehydrogenation; it can be decarboxylated to γ -aminobutyrate, and its

* Present address: Sir William Dunn School of Pathology, University of Oxford.

carbon skeleton can be synthesized from glucose and intermediates of glucose metabolism (see Waelsch & Lajtha, 1961; Beloff-Chain, Catanzaro, Chain, Masi & Pocchiari, 1955; Kini & Quastel, 1959; Chain, Cohen & Pocchiari, 1962; Sellinger, Catanzaro, Chain & Pocchiari, 1962; Krebs & Bellamy,

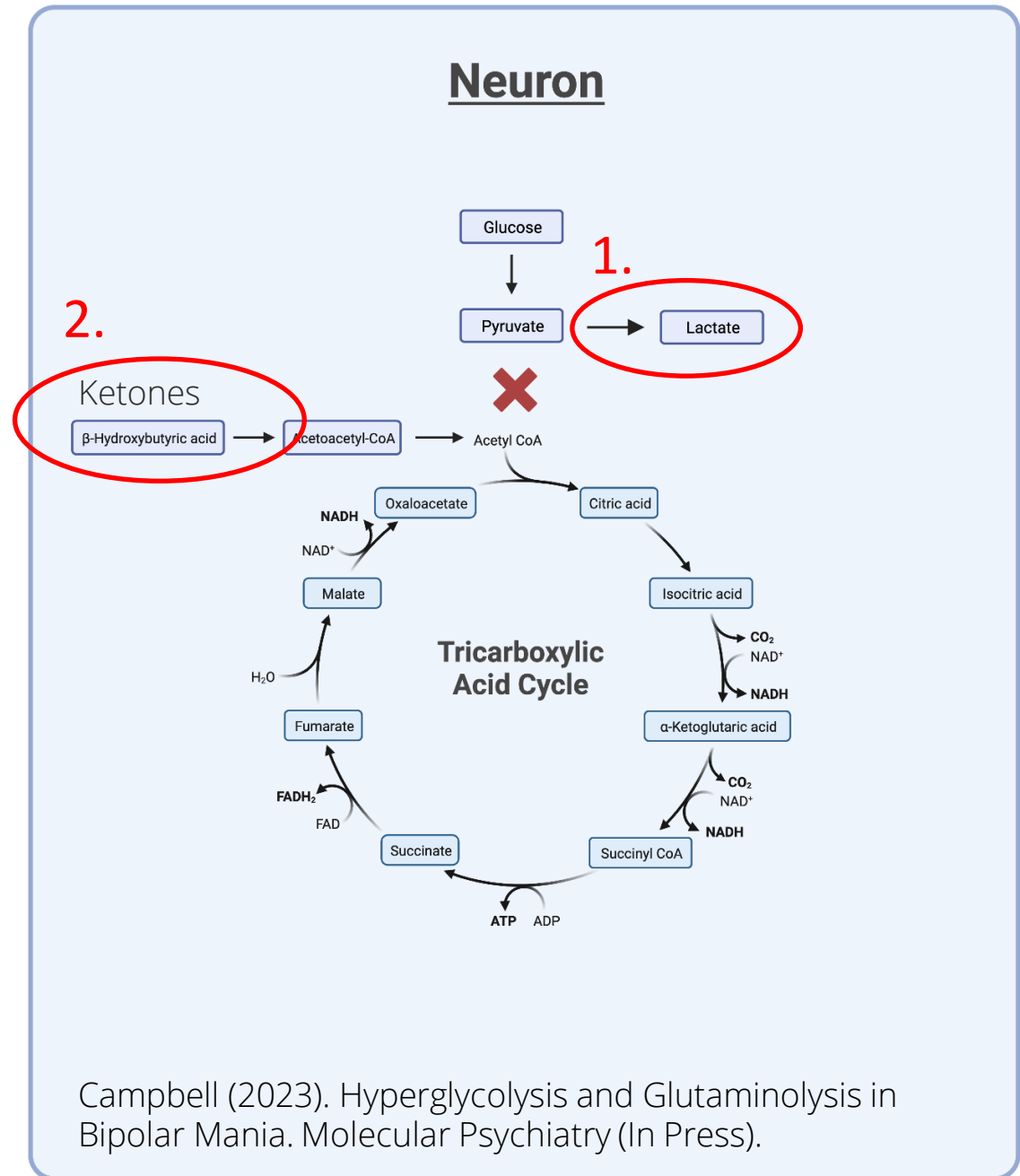
Energy Dysregulation in BD

1. Increased lactate, indicating impaired glucose metabolism.

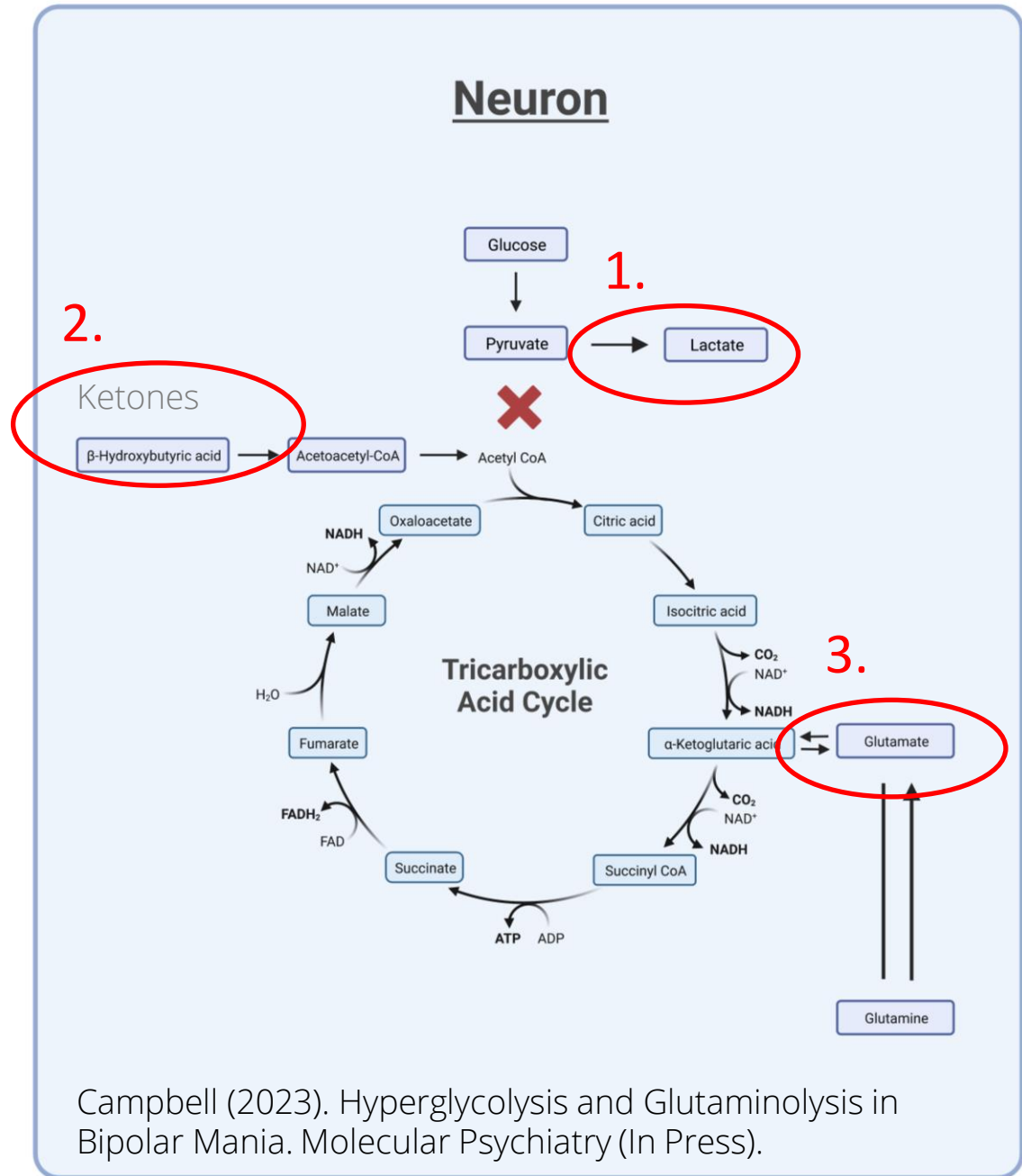


Campbell (2023). Hyperglycolysis and Glutaminolysis in Bipolar Mania. *Molecular Psychiatry* (In Press).

1. Increased lactate indicating, impaired glucose metabolism.
2. Ketones act as an alternative fuel source to restore energy (ATP).



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2. Ketones act as an alternative fuel source to restore energy (ATP).
3. Glutamate can also be used as a significant alternative energy source in neurons.

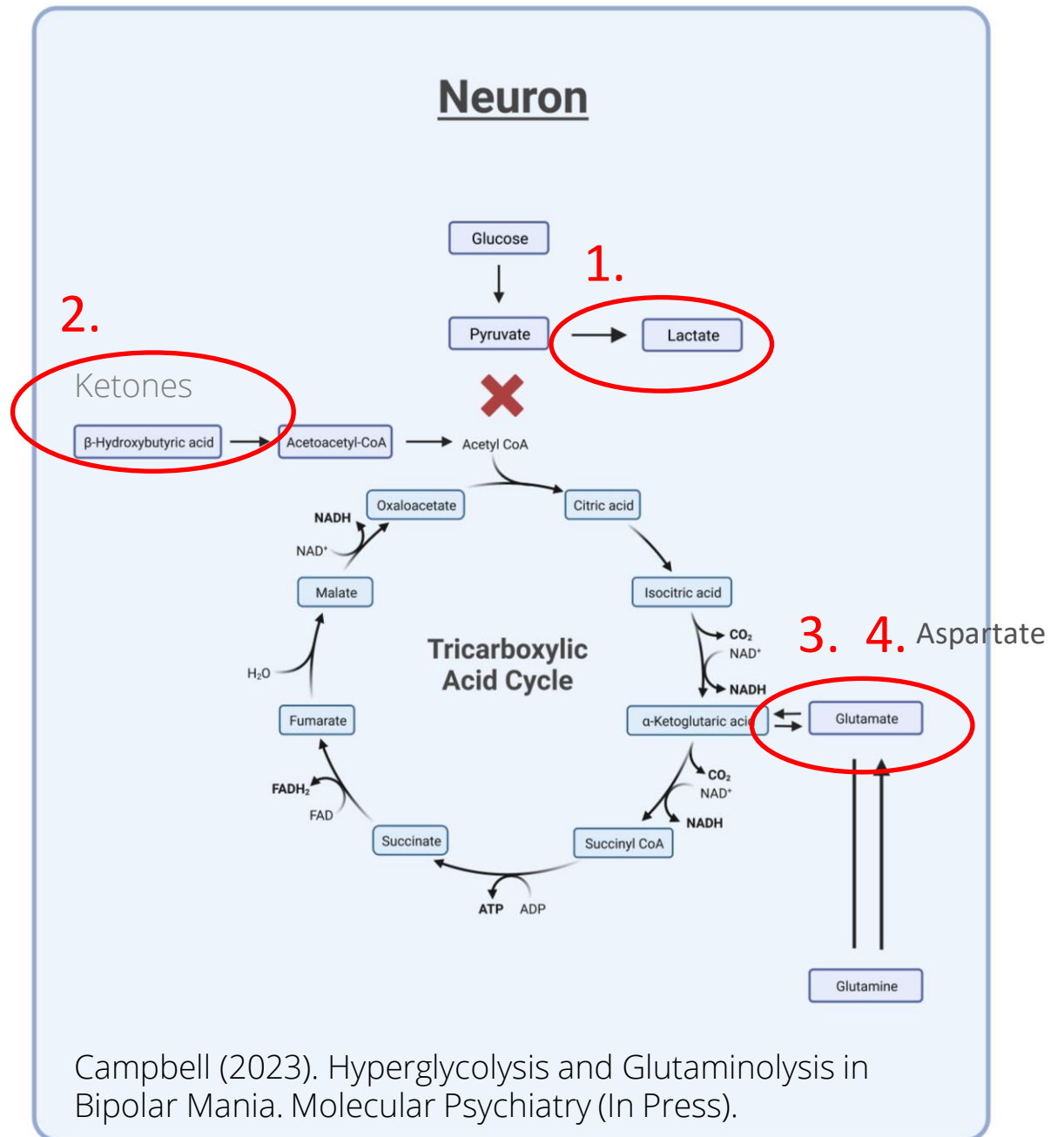


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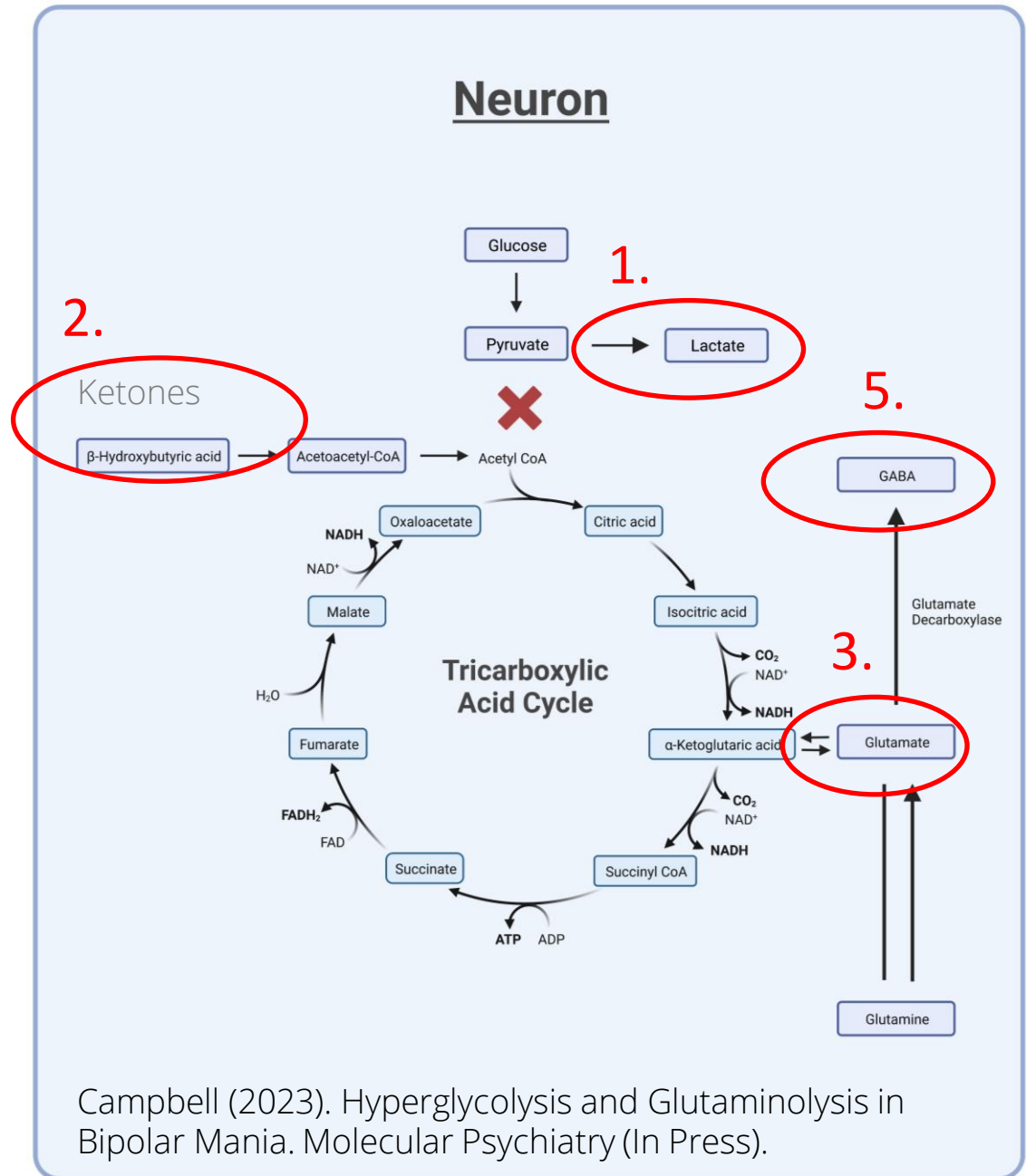
2. Ketones act as an alternative fuel source to restore energy (ATP).

3. Glutamate can *also* be used as a significant alternative energy source in neurons.

4. Aspartate participates in the transamination reaction converting glutamate to krebs cycle intermediate alpha-ketoglutarate.

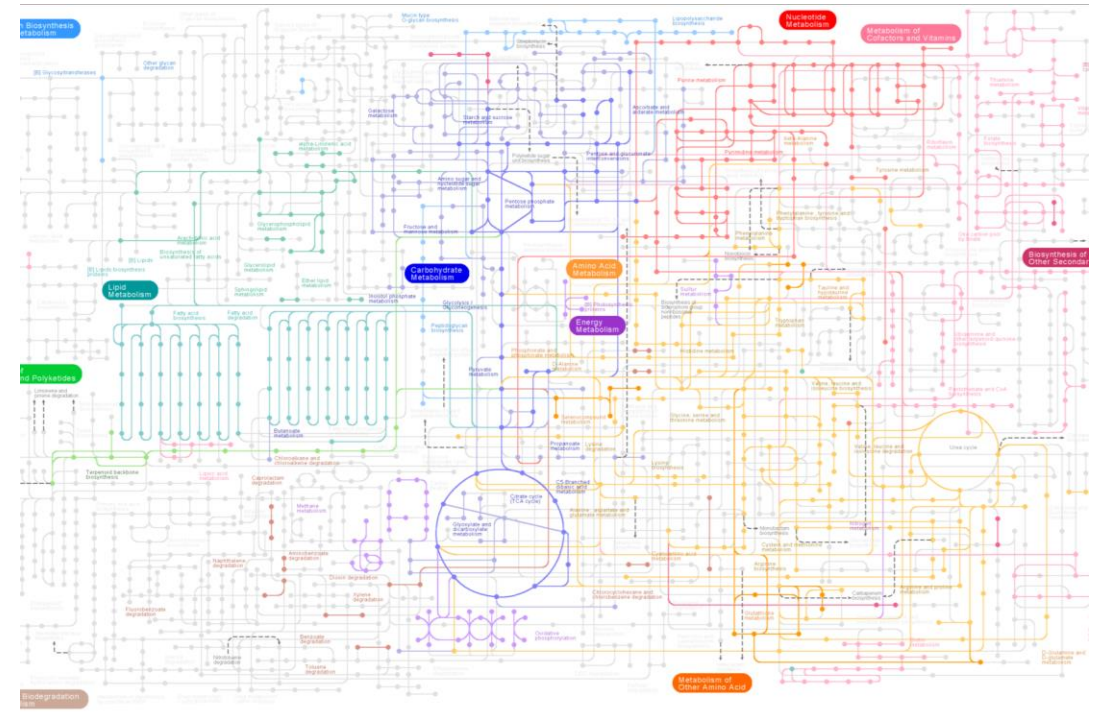


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3. Glutamate can *also* be used as a significant alternative energy source in neurons.
4. Aspartate is participates in the transamination reaction converting glutamate to krebs cycle intermediate alpha-ketoglutarate.
5. Ketones may preclude the need to upregulate glutamate metabolism and promote increased GABA.



Summary

- Bipolar Disorder shares anti-seizure medications with epilepsy.
- A metabolic therapy for epilepsy (ketogenic diet) is now showing indications of beneficial effects in bipolar disorder.
- Ketosis causes a shift from excitatory brain activity toward inhibitory activity by reducing glutamate metabolism and increasing GABA.
- These are relevant mechanisms for both epilepsy and bipolar disorder. Glutamatergic mechanisms are a primary target of several anti-seizure medications.
- Ketogenic diet can confer concomitant physical and mental health benefits. It also has potential as a powerful preventative measure.



- Neurometabolism

The Metabolic Overdrive Hypothesis. Hyperglycolysis and Glutaminolysis in Bipolar Mania.

Campbell I, Campbell H

Preprint from PsyArXiv, 24 May 2023

<https://doi.org/10.31234/osf.io/48dba> PPR: PPR667056

Preprint

Thank you

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iain.campbell@ed.ac.uk
[@iaincampbellphd](https://twitter.com/iaincampbellphd)