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## DEFINING THE POTENTIAL ANTIDEPRESSANT MODE OF ACTION OF ACETYL-L-CARNITINE: A TANTALIZING TASK

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Bigio et al (1) report that oral administration of acetyl-L-carnitine (ALC) results in antidepressant-like effects along with an improvement of energy metabolism in the vDG in endogenously depressed Flinders Sensitive Line rats (FSL). FSL also show a significant reduction of ALC in the hippocampus and prefrontal cortex compared to Flinders Resistant Line rats (FRL). However, it is not clear whether such deficiency is associated with alterations in the free carnitine concentration, or whether such changes in ALC concentrations also occur in other brain regions. In addition, the study did not show whether the ALC-mediated antidepressant effect was linked to a correction of a *prior* ALC deficiency in these two brain regions. Interestingly, only a subset of FSL animals responded to ALC, although both FSL responders and non-responders were ALC deficient. It is unclear whether ALC deficiency is pathogenic for this mood disorder and/or whether oral administration of ALC corrects a pre-existing deficiency.

Orally administered ALC is poorly bioavailable, and is subjected to a fast renal clearance (less than 10% is reabsorbed). In addition, owing to the presence of carnitine acetyltransferase (CrAT), an enzyme catalyzing the transesterification of acetyl-CoA and acetylcarnitine in the mitochondrial matrix and peroxisomes, the C2 moiety in ALC would be efficiently processed by the gut and the liver to supplement their respective acetyl-CoA pools, with the release of free carnitine. Therefore, brain exposure to ALC is expected to be very low. Moreover, since ALC also acts as a prodrug of carnitine, it would have been appropriate to perform experiments with FSL animals orally treated with L-carnitine. Since it has been shown that ALC may exert pharmacologic effects independently of its metabolism (to acetyl-CoA and carnitine), it would be important to exclude a metabolism-independent effect, e.g. by treating FSL rats with D-acetylcarnitine.

The authors suggest that ALC-mediated antidepressant action is linked to improved insulin sensitivity in FSL animals. Therefore, it would have been instructive to know if treatment with well-established insulin-sensitizers (e.g. glitazones) could have ameliorated mood disorder in the FSL, particularly

non-responders. Considering that diabetes significantly raises blood ALC levels, it would be anticipated that this condition would also have an antidepressant effect – which can be tested in animals, but which is not expected to be borne out in humans, in whom diabetes is frequently associated with depression.

An epigenetic mechanism was proposed for ALC action, implying a pathway leading from extracellular ALC to nuclear acetyl-CoA, and acetylation of HRK. This assumes the existence of a nuclear CrAT as suggested in (2). Currently strong evidence for nuclear acetyl-CoA formation comes from observations on a nuclear ATP citrate lyase and nuclear pyruvate dehydrogenase complex (3).

## References

- (1) Bigio, B, Matthe, AA, Sousa, VC et al (2016) *Epigenetics and energetics in ventral hippocampus mediate rapid antidepressant action: Implications for treatment resistance* Proc Natl Acad Sci USA, **113**, 7906-11
- (2) Madiraju, P, Pande, SV, Prentki, M & Madiraju, SR (2009) *Mitochondrial acetylcarnitine provides acetyl groups for nuclear histone acetylation* Epigenetics **4**, 399-403.
- (3) Sutendra, G, Kinnard, A, Dromparis, P et al (2016) *A nuclear pyruvate dehydrogenase complex is important for the generation of acetyl-CoA and histone acetylation* Cell **158**, 84-97