LETTER

Defining the potential antidepressant mode of action of acetyl-L-carnitine

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Bigio et al. (1) report that oral administration of acetyl-L-carnitine (LAC) results in antidepressant-like effects along with an improvement of energy metabolism in the ventral dentate gyrus in endogenously depressed Flinders Sensitive Line rats (FSL). FSL also show a significant reduction of LAC in the hippocampus and prefrontal cortex compared with Flinders Resistant Line rats (2). However, it is not clear whether such deficiency is associated with alterations in the free carnitine concentration, or whether such changes in LAC concentrations also occur in other brain regions. In addition, the study (1) does not show whether the LAC-mediated antidepressant effect is linked to a correction of a prior LAC deficiency in these two brain regions. Interestingly, only a subset of FSL animals responded to LAC, although both FSL responders and nonresponders were LAC deficient. It is unclear whether LAC deficiency is pathogenic for this mood disorder or whether oral administration of LAC corrects a preexisting deficiency.

Orally administered LAC is poorly bioavailable and is subjected to a fast renal clearance (3). In addition, because of the presence of carnitine acetyltransferase (CrAT), an enzyme catalyzing the transesterification of acetyl-CoA and LAC in the mitochondrial matrix and peroxisomes, the C2 moiety in LAC would be efficiently processed by the gut and the liver to supplement their respective acetyl-CoA pools, with the release of free L-carnitine (3). Therefore, brain exposure to LAC is expected to be very low. Moreover, because LAC also acts as a prodrug of L-carnitine and because L-carnitine treatment elevates endogenous LAC (3, 4), it would have been appropriate to perform experiments with FSL animals orally treated with L-carnitine. Because it has been shown that LAC may exert pharmacologic effects independently of its metabolism (to acetyl-CoA and carnitine), it would be important to exclude a metabolism-independent effect: for example, by treating FSL rats with acetyl-D-carnitine (5).

Bigio et al. (1) suggest that LAC-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 nonresponders. Considering that diabetes significantly raises blood LAC levels (6), 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 (7).

An epigenetic mechanism was proposed for LAC action, implying a pathway leading from extracellular LAC to nuclear acetyl-CoA, and acetylation of H3K27 (2). This proposal assumes the existence of a nuclear CrAT, as suggested in ref. 8, because CrAT is absent from the cytosolic compartment (9). Currently, strong evidence for nuclear acetyl-CoA formation comes from observations on a nuclear ATP citrate lyase and a nuclear pyruvate dehydrogenase complex (10). Whether epigenetics and energetics factors may mediate the antidepressant-like effects of LAC remains to be determined.

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