Title
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Journal
American Journal of Geriatric Psychiatry, 26(6)

ISSN
1064-7481

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Publication Date
2018-06-01

DOI
10.1016/j.jagp.2018.03.014

Peer reviewed

Response to Letter About Memory and Brain Effects of Curcumin

TO THE EDITOR:

Considerable disagreement exists on the necessity and extent of adjustment for multiple comparisons.[1] Although many articles have discussed when and how to control for inflation of Type I errors (i.e., finding a difference between groups when none exists), there is no consensus in the literature regarding this issue.[2–4] It has been pointed out, however, that adjustment is not required when the research is addressing novel or exploratory hypotheses—that is, when one also needs to consider the risk of making a Type II error (i.e., finding no difference when one exists).[2,5] Adjusting only for Type I error increases the risk for Type II error.[6]

Schulz and Grimes[7] recommend restricting the number of primary end points tested and confining significance testing to only those hypotheses specified beforehand. If such primary outcomes have been specified beforehand, then correcting for multiplicity may be too conservative and should be avoided. As detailed in our report,[8] we specify our primary (Buschke Selective Reminding Test for verbal memory, Brief Visual Memory Test-Revised for visual memory) and secondary (Trail Making Test Part A) outcome measures and then present results for these prespecified outcome measures without correction. Further, we point out that we did not correct for multiple tests because this was a pilot study, thus following the recommendation of Streiner and Norman,[1] who note that exploratory studies addressing a small number of hypotheses do not require such corrections. Moreover, by emphasizing effect sizes in our results, the multiplicity problem further diminishes in impact.

Regarding the comments about between-group differences, these are typically the primary metric by which the results of a clinical trial are evaluated; however, as has been noted, both in the case when the primary outcome is positive[9] and when the primary outcome fails,[10] a more detailed examination of the totality of the evidence is warranted. Within-group changes are both informative and clinically relevant, especially in the context of a pilot study. By presenting all results, which we clearly indicate as between-group or within-group, readers are provided all relevant information regarding within-treatment as well as between-treatment outcome variability and can therefore make their own judgment as to the clinical significance of the treatment.

Dcruz et al. also comment that the low dropout rate in our study suggests that the sample is atypical, although other clinical trials using supplements with minimal side effects in people with mild age-related memory complaints[11] have demonstrated comparably low dropout rates.

Our interpretation that FDDNP binding reflects brain accumulation of both amyloid and tau neuroaggregates was also questioned by citing research based on computer simulations examining FDDNP binding to Aβ fibrils and Aβ monomers, resolved from solid-state nuclear magnetic resonance experiments.[12] A cursory reading of this research suggests that the authors established three conclusions:

(a) Their computer simulations suggest that FDDNP ligands bind with high affinity to Aβ fibrils —as already demonstrated experimentally with in vitro fibril determinations, X-ray crystallography, and human brain tissue specimens, as well as positron emission tomography in the brain of living subjects.[13–18] Moreover, hydrophobic effects coupled with π-stacking interactions are the dominant factors governing FDDNP binding.[16]

(b) FDDNP binds to two distinct sites on the Aβ fibril.

(c) Computer simulations reveal a strong tendency of bound FDDNP molecules for self-aggregation at millimolar (32 mM) FDDNP concentrations, which were used for these computer simulations. These concentrations are more than 10^6 to 10^9 times higher than the concentrations of FDDNP (or other PET ligands) used in in vitro or in vivo experiments, which explains the suggestion for possible FDDNP binding to Aβ monomers, facilitated by aggregation, which typically occurs at high concentrations (e.g., $>10^{-4}$ M).

Using an integrated approach including molecular docking, molecular dynamics, and energy calculations to investigate site-specific interactions of different amyloid binding molecules, Murugan et al.[19] recently further confirmed experimental evidence of FDDNP binding to Aβ fibrils.

We have no direct evidence that FDDNP can bind curcumin in vivo or that curcumin may interfere with the FDDNP PET signal. Nevertheless, it is essential to consider and exclude any possible interactions between the probe under investigation and any pharmacological agent used by the research subjects at the time of the PET determination. As we note in our report, we are not certain how curcumin may exert cognitive and mood effects, and curcumin's very low brain permeability points to factors other than direct amyloid or tau binding as more likely explanations for curcumin's brain health effects. Abundant evidence indicates that curcumin's in vivo central effect of reducing amyloid accumulation might derive from multiple activities beyond direct binding inhibition of aggregate formation. These curcumin effects may be mediated through the gut-controlled inflammatory processes in the body, involving multiple pathways such as metal chelation; limitation of oxidative damage; and reduction of cholesterol, proinflammatory cytokines, and lipids.[8] In support of an anti-inflammatory mechanism is a very recent study showing that curcumin prevented acute neuro-inflammation and long-term memory impairment in laboratory mice.[20]

We have been cautious in interpreting these observed curcumin benefits and have stressed that the relatively small sample size in our study warrants caution in interpreting our results. The finding that curcumin consumption compared with placebo benefits clinical symptoms is consistent with our a priori hypotheses, and the observation that it independently leads to less FDDNP binding in two key components of the limbic system—the amygdala and the hypothalamus—further supports these cognitive findings, however. The role of the amygdala in memory processing, decision-making, and emotional responses, in conjunction with the role of the hypothalamus in the innervation of cortical regions involved in Alzheimer disease, cannot be ignored or dismissed. A future study in a larger sample would certainly provide additional insight on curcumin's effects on memory and its mode of action.

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