LETTER

Reply to Belmaker *et al*.: GSK3β haploinsufficiency results in lithium-like effects in the forced-swim test

Belmaker *et al*. (1) point out that in our recent PNAS article (2) we did not cite a study (3) in which haploinsufficient GSK3β (GSK3$\beta^{+/-}$) mice on a C57BL/6J background phenocopied behavioral outcomes of lithium treatment. This omission does not imply that our results support the inability of Belmaker *et al*. to reproduce the data of O'Brien *et al.* (3). In our study, we performed the tail suspension (2) as part of a battery of tests to examine the contribution of GSK3β to behavioral abnormalities resulting from low serotonin synthesis. Our results indicate that reduced GSK3β expression affected this behavioral paradigm only in mice with low serotonin (2, 4). Because we used a different behavioral test (tail suspension versus forced-swim test) and GSK3$\beta^{+/-}$ mice of a different genetic background, we do not consider that our results directly contradict those of O'Brien *et al*. Furthermore, in the forced-swim test, GSK3$\beta^{+/-}$ mice of the same genetic background as those used by O'Brien *et al*. display significant "antidepressant-like" effect as compared with their WT littermates [immobility times: 266 $\pm$ 19 sec/4 min (WT) and 138 $\pm$ 22 sec/4 min (GSK3$\beta^{+/-}$); $P \leq 0.001$ (*t* test); $n = 10$ mice per group], indicating that these data are replicable. Although GSK3$\beta^{+/-}$ mice are useful to reveal the contribution of GSK3 to some behaviors (2, 3, 5, 6), these mice express normal levels of GSK3α and show only an $\approx$25% reduction in total GSK3 activity (5). Therefore, phenotypes observed in GSK3$\beta^{+/-}$ mice may be more sensitive to variations in experimental conditions than those obtained with lithium that will affect both GSK3 isoforms (5, 7).

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The authors declare no conflict of interest.

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