LETTER

Reply to Schmidt *et al.*: The long and the short of BAG1

Schmidt *et al.* (1) have raised an important point, and we are pleased to be able to respond and provide clarification. They suggest that the BAG1S form (which was overexpressed in these mice) does not inhibit glucocorticoid receptors (GRs) and that the phenotypes that we observe in our BAG1-overexpressing mice (2) are thus not likely to be correlated to a disturbed GR and stress system. Below we cite evidence to support our article's assertion. Kanelakis *et al.* (3) found that overexpressed BAG1S was able to inhibit GR function depending on the ratio of BAG1S proteins to Hsp70/Hsc70. Because BAG1 was overexpressed in our mice, it may be continuously bound to Hsp70 and thus able to block GR function (3). Furthermore, Schneikert *et al*. [in a paper cited by the authors (4)] discuss whether BAG1 may have different effects on hormone binding by GRs due to differences in the ratio of BAG1 proteins to Hsp70/Hsc70. Clearly, this may be the case for BAG1-overexpressing mice. Second, BAG1S may compete with common targets for BAG1M and BAG1L, thus freeing these isoforms to inhibit GR function. Third, BAG1S may directly interact with the Hsp70, Hsp90, p60/Hop, Hsp-40-GR complex at high concentrations and inhibit GR function. Given that BAG1's regulation of GRs is still being elucidated, it seems unreasonable to rule out a potential role for BAG1S in disrupting the GR and stress system. However, we appreciate the comments by Schmidt *et al*. (1), which help illuminate this issue and highlight topics for continuing research.

***Husseini Manji*[a] *and Bruce S. McEwen*[b,1]**

[a]*Mood and Anxiety Disorders Program, National Institute of Mental Health, Bethesda, MD 20892–9663; and* [b]*The Rockefeller University, New York, NY 10021-6399*

1. Schmidt U, *et al*. (2008) Role of the hsp70 cochaperone BAG1 in glucocorticoid receptor function and stress-related diseases. *Proc Natl Acad Sci USA* 10.1073/pnas/0803736105.
2. Maeng S, *et al*. (2008) *BAG1* plays a critical role in regulating recovery from both manic-like and depression-like behavioral impairments. *Proc Natl Acad Sci USA* 105:8766–8771.
3. Kanelakis KC, *et al*. (1999) Differential effects of the hsp70-binding protein BAG-1 on glucocorticoid receptor folding by the hsp90-based chaperone machinery. *J Biol Chem* 274:34134–34140.
4. Schneikert J, *et al*. (2000) Hsp70-RAP46 interaction in downregulation of DNA binding by glucocorticoid receptor. *EMBO J* 19:6508–6516.

Author contributions: H.M. and B.S.M. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. E-mail: mcewen@mail.rockefeller.edu.

www.pnas.org/cgi/doi/10.1073/pnas.0810014105