Reviewer's report

Title: Recent advances in the molecular mechanisms determining tissue sensitivity to glucocorticoids: novel mutations, circadian rhythm and ligand-induced repression of the human glucocorticoid receptor

Version: 2
Date: 18 July 2014
Reviewer: Thomas Dickmeis

Reviewer's report:

The authors have answered all of my previous requests, and I see no further obstacles for publication. I have only minor suggestions for changes upon reading the revised manuscript.

Minor essential revisions:

1) Page 2 line 10: remove comma after “diversity”
2) Page 4 line 6: add “a” after “presence of”
3) Page 5 line 1: add comma after “genes” and “the GR” after “and”
4) Page 5 line 4: replace “quadrimetric” with “tetrameric”
5) Page 8 line 10: add “the” after “addition to”
6) Page 8 line 19: add “circadian” after “‘clock’, the”
7) Page 8 line 23: add “directly” after “does not” (some indirect feedback of glucocorticoids on the central clock may occur via an indirect pathway involving serotonergic projections from the raphe nuclei, see Buijs and Escobar, 2007)
8) Page 9 line 14: add “influence” after “central clock”
9) Page 12 line 21: add “which” after “epigenetic modifications”

Discretionary revisions:

1) Page 9 line 23, “Instead,…”: I am still not sure I understand everything correctly here. DUSP and TNFalpha do not show circadian oscillations either in vivo or in the absence of cortisol (i.e. in charcoal treated medium) in vitro. However, they do show a circadian difference in responsiveness to cortisol treatment in vitro that would be consistent with CLOCK-mediated GR-acetylation effects. I would suggest re-phrasing this part of the manuscript as follows:

“[…], diurnal mRNA fluctuations in vivo nor did they oscillate in the absence of cortisol in vitro. However, they did respond differentially to glucocorticoid treatment at different times in vitro, fitting to the temporal pattern of GR acetylation observed in the cultures. These findings […] evening and early night. For some glucocorticoid-responsive genes, these opposing effects of circadian cortisol level changes and CLOCK-mediated GR acetylation might cancel each other out, leading to non-oscillating expression in vivo despite oscillating
glucocorticoid levels.”

Reference:

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.