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Adenylyl cyclases types 1 and 8 promote pro-survival pathways after ethanol exposure in the neonatal brain

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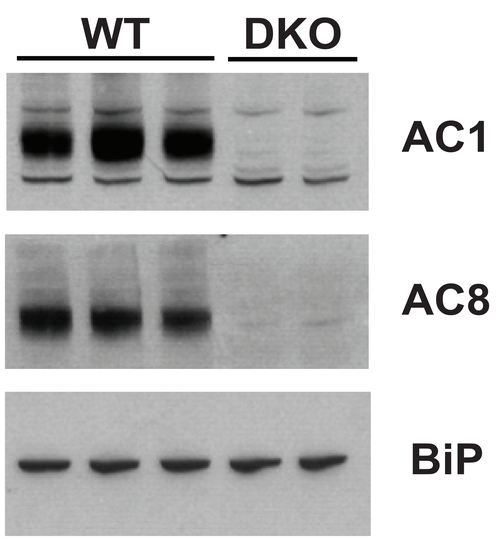
Introduction

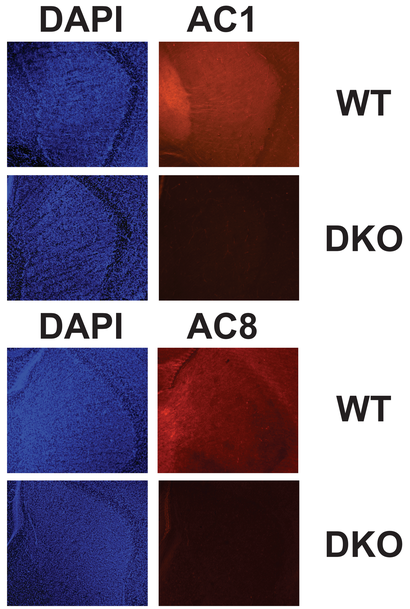
- A wide range of developmental disabilities following fetal alcohol exposure is observed clinically, however, the molecular factors that determine the severity of these sequelae remain undefined.
- Deletion of adenylyl cyclases (ACs) 1 and 8 exacerbates the neuroapoptosis that occurs in the delayed period after ethanol exposure; however, it remains unclear whether AC1 and AC8 are critical to the primary or secondary mechanisms underlying ethanol-induced neurodegeneration.
- In order to examine this distinction, P7 WT and AC1/AC8KO (DKO) mice were given one injection of saline or ethanol (5.0 g/kg) and their striata were examined in the acute post-treatment period (1-4 hrs) to assess the activation of both caspase-3 and pro-survival mechanisms.

Results

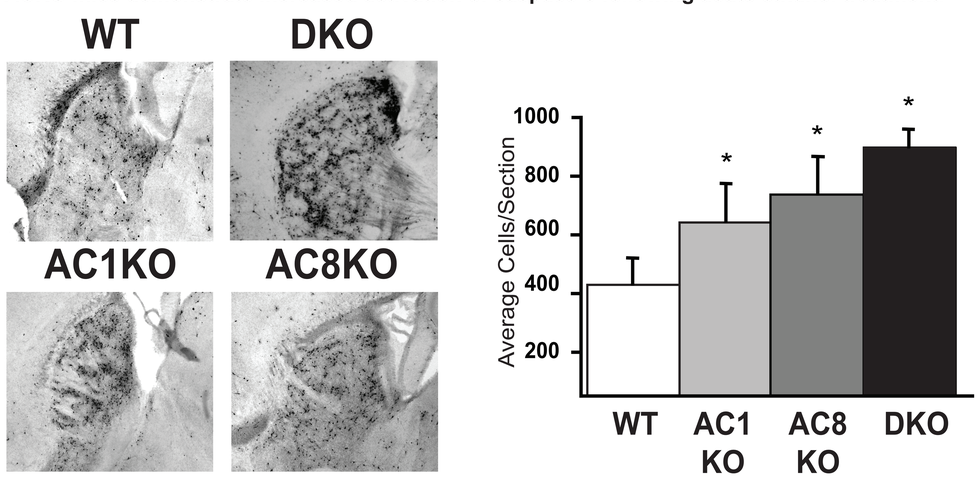
1. Abundant protein expression of AC1 and AC8 is detected in membrane-enriched striatal protein extracts obtained from P7 WT and DKO mice.



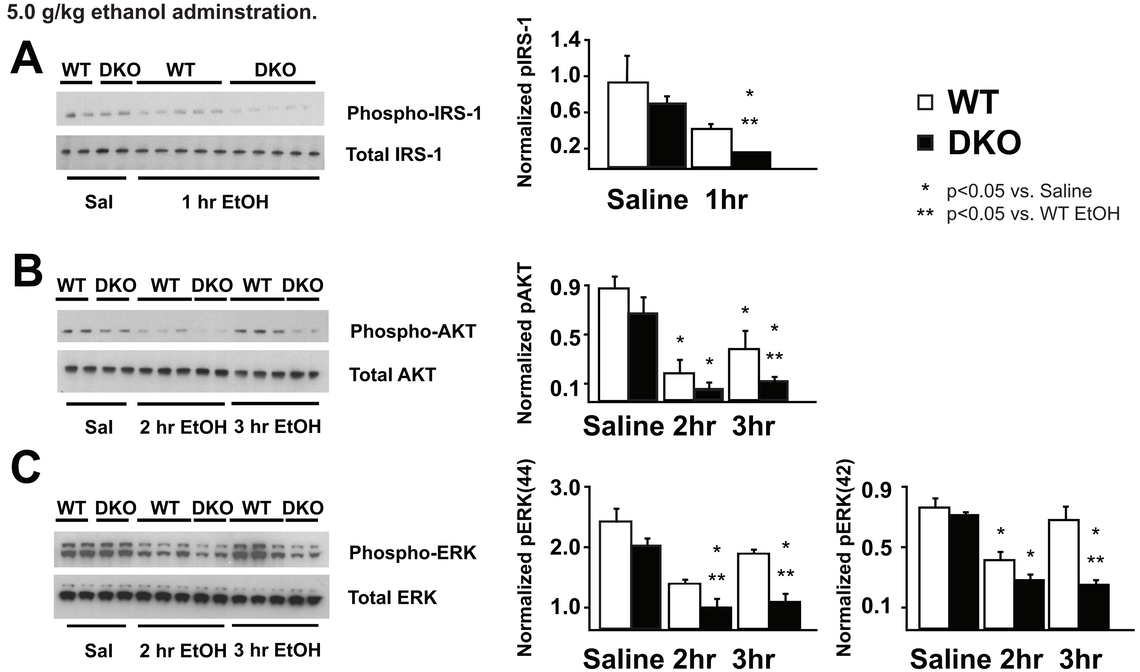
2. Representative sagittal sections from the P7 mouse brain demonstrate widespread protein distribution of AC1 and AC8.



3. ACKO mice demonstrate increased activation of caspase-3 following acute ethanol treatment.



4. DKO mice demonstrate impaired pro-survival protein phosphorylation in the striatum acutely following 5.0 g/kg ethanol adminstration.



Conclusions

- Deletion of AC1 and AC8 exacerbates the neuroapoptotic response in the striatum acutely following a single ethanol exposure.
- Pro-survival signaling involving phosphorylation of IRS-1, Akt and ERK is impaired in DKO mice following ethanol treatment.
- Variation in activity of AC1 and AC8 may have important ramifications for the likelihood of a fetus' susceptibility to FAS.

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