Glucocorticoids target postnatal oligodendrocyte precursor cells differentiation and stress-induced behavior in a sex-specific manner

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1 Background

Oligodendrocyte precursor cells (OPCs) modulate neuronal activity and respond to environmental hazards. OPCs can differentiate into myelinating oligodendrocytes (OLs), but a large portion of OPCs stay undifferentiated. Expression of glucocorticoid receptors (GRs) of OPCs in various areas of the brain suggests a physiological role of glucocorticoid (GC) in OPC function and differentiation. To observe the role of GCs in modulating OPC maturation and long-term behavioral phenotyping, conditional knock-out (cKO) of GR in OPCs was done, in tandem with a battery of behavioral tests.

2 Methods & Results

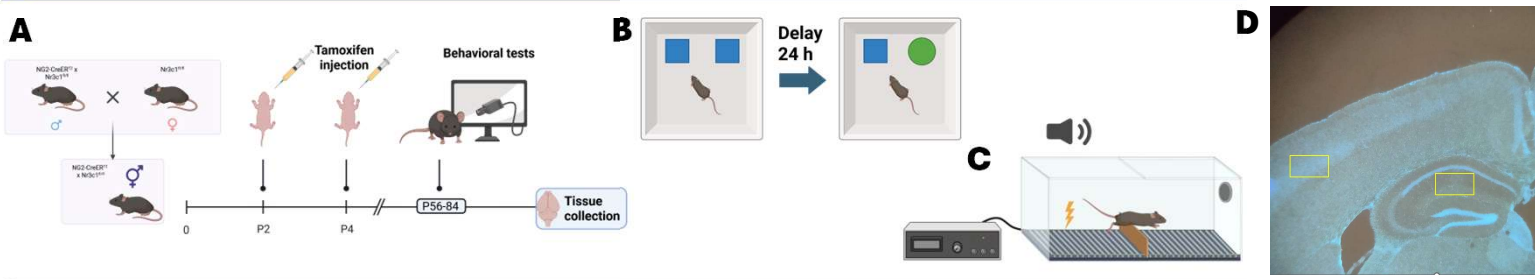
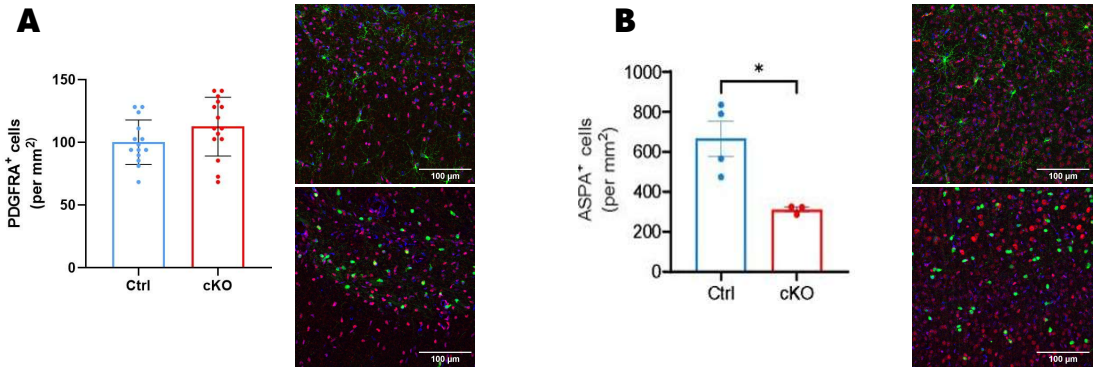
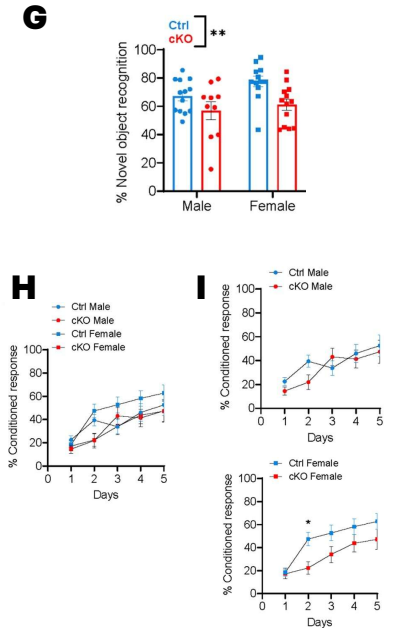


Fig 1. (A): Breeding strategy and experimental timeline for GR deletion via tamoxifen injections; (B): Illustration of the novel-object recognition test; (C) Illustration of the two-way active avoidance test; (D) Regions of interest (ROIs, Cornu ammonis 1 & somatosensory cortex)

Effect of GR deletion on cell density



Behavioral data



Colocalization of GR in OPCs and mature OLs

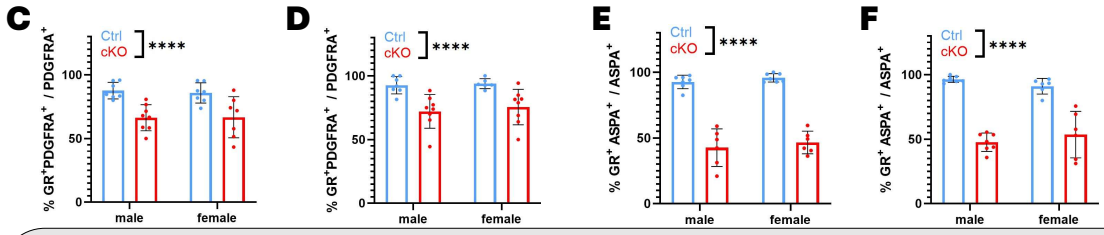


Fig 2:
(A): Density of PDGFRA+ cells per cubic mm in the CA1 region (left) and representative confocal images of the co-expression of GR(red) and OPC (green) in the CA1 (top right) and cortex (bottom right);
(B): Density of ASPA+ cells per cubic mm in the CA1 region (left) and representative confocal images of the co-expression of GR(red) and OL (green) in the CA1 (top right) and cortex (bottom right) (unpaired t test with Welch's correction: t(3.129) = 4.038, p = 0.0252; n = 4 Ctrl and n = 5 cKO mice);
(C): % of colocalized GR+PDGFRA+ cells compared to the total number of PDGFRA+ cells in CA1, (Two-way ANOVA: genotype, F(1, 25) = 25.15, p < 0.0001; n = 7M/7F Ctrl and n = 8M/7F cKO);
(D): % of colocalized GR+PDGFRA+ cells compared to the total number of PDGFRA+ cells in cortex, (Two-way ANOVA: genotype, F(1, 25) = 23.08, p < 0.0001; n = 7M/6F Ctrl and n = 8M/8F cKO);
(E): % of colocalized GR+ASPA+ cells compared to the total number of ASPA+ cells in CA1, (Two-way ANOVA: genotype, F(1, 22) = 217.9, p < 0.0001; n = 7M/7F Ctrl and n = 6M/6F cKO);
(F): % of colocalized GR+ASPA+ cells compared to the total number of ASPA+ cells in cortex, (Two-way ANOVA: genotype, F(1, 22) = 123.1, p < 0.0001; n = 7M/6F Ctrl and n = 7M/6F cKO);
(G): Percentage index (%) for two identical objects (Two-way ANOVA: genotype, F(1,44) = 10.02. p = 0.0028; n = 13M/12F Ctrl and n = 10M/13F cKO);
(H): % of conditioned response over days in both sexes (Three-way ANOVA: genotype x day x sex, F (4, 224) = 2.555, p = 0.0398; n = 17M/16F Ctrl and n = 12M/15F cKO)
(I): % of conditioned response over days in both sexes in males (top, Two-way RM ANOVA: days x genotype, F(4, 108) = 2.664, p = 0.0363; Šídák's multiple comparisons test: day 2: cKO = Ctrl) and females (bottom, Two-way RM ANOVA: days x genotype, F(4, 116) = 3.010, p = 0.021; Šídák's multiple comparisons test: day 2: cKO < Ctrl, p = 0.0339; n = 17M/16F Ctrl and n = 12M/15F cKO)

3 Conclusions

Postnatal deletion of GR in OPCs resulted in a slight, non-significant increase in OPC density, but a reduced density in mature OLs, particularly in the hippocampus in adulthood. The highly significant decrease in GR+ASPA+ cells, both in CA1 and in the somatosensory cortex, suggest a reduced proliferation and/or reduced survivability of in OPCs due to the cKO of GRs therein. Behavioral results show impaired memory and aversive learning tasks but did display alteration in anxiety and sociability in adulthood. The cKO mice displayed significantly lower performance in novel object recognition compared to control mice, for both sexes. In the active avoidance learning test, female cKO mice were significantly worse on day 2, requiring more trials to learn the task compared to the control mice.

To conclude, data suggests that GRs play an important role from the very early stages of postnatal development in regulating OL differentiation. Absence of GR results in impairment of learning abilities, particularly under mild stress.

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