The P2X7 receptor contributes to seizures and inflammation-driven long-lasting brain hyperexcitability following neonatal hypoxia in mice

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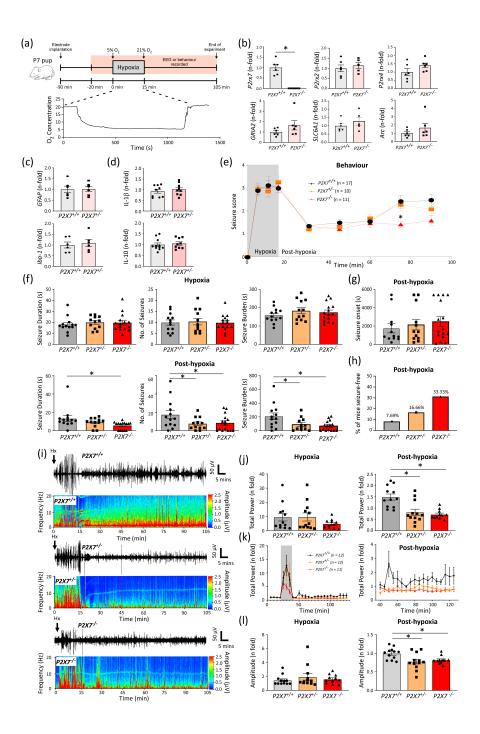
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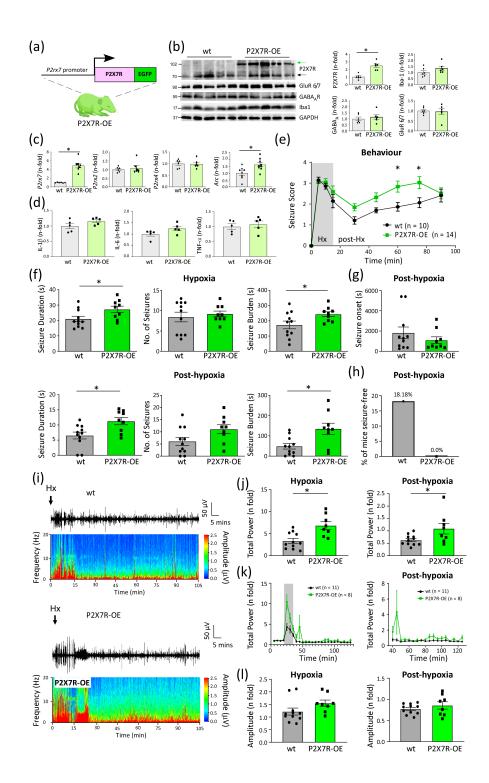
Abstract

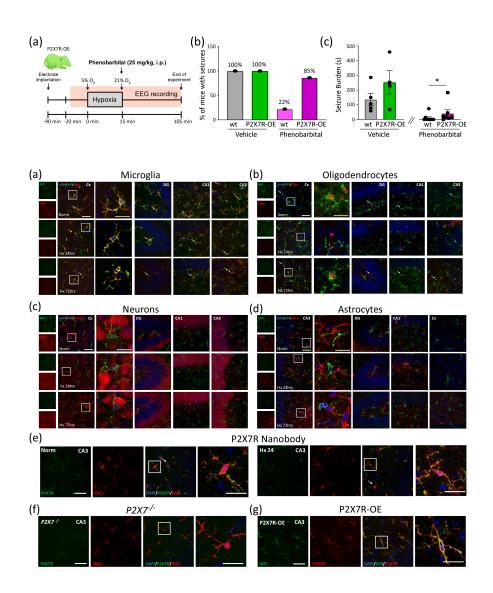
Background and Purpose Neonatal seizures are a clinical emergency. Current anti-seizure medications, however, fail to resolve seizures in ~50% of infants. The P2X7 receptor (P2X7R) is an important driver of inflammation and evidence suggest P2X7R contributing to seizures and epilepsy in adults. To date, however, no genetic proof has been provided to determine the contribution of the P2X7R to neonatal seizures, its effects on inflammatory signalling during neonatal seizures and the therapeutic potential of P2X7R-based treatments on long-lasting brain excitability. Experimental Approach Neonatal seizures were induced via global hypoxia in 7 day-old mouse pups (P7). The role of P2X7Rs during seizures was analyzed in P2X7R overexpressing and knock-out mice. Treatment of wild-type mice post-hypoxia with the P2X7R antagonist JNJ-47965567 was used to determine the effects of the P2X7R on long-lasting brain hyperexcitability. Cell type-specific P2X7R expression was analyzed via P2X7R-EGFP reporter mice. RNA sequencing was used to monitor P2X7R-dependent hippocampal down-stream signalling. Key Results P2X7R deletion reduced seizure severity whereas P2X7R overexpression exacerbated seizure severity and reduced responsiveness to anti-seizure medication. P2X7R deficiency let to an anti-inflammatory phenotype in microglia and treatment of mice with a P2X7R antagonist reduced long-lasting brain hyperexcitability. RNA sequencing identified several pathways altered in P2X7R knock-out mice after neonatal hypoxia including a down-regulation of genes implicated in inflammation and glutamatergic signalling. Conclusion and Implications Treatments based on targeting the P2X7R may represent a novel therapeutic strategy for neonatal seizures with P2X7Rs contributing to the generation of neonatal seizures, driving inflammatory processes and long-term hyperexcitability states.

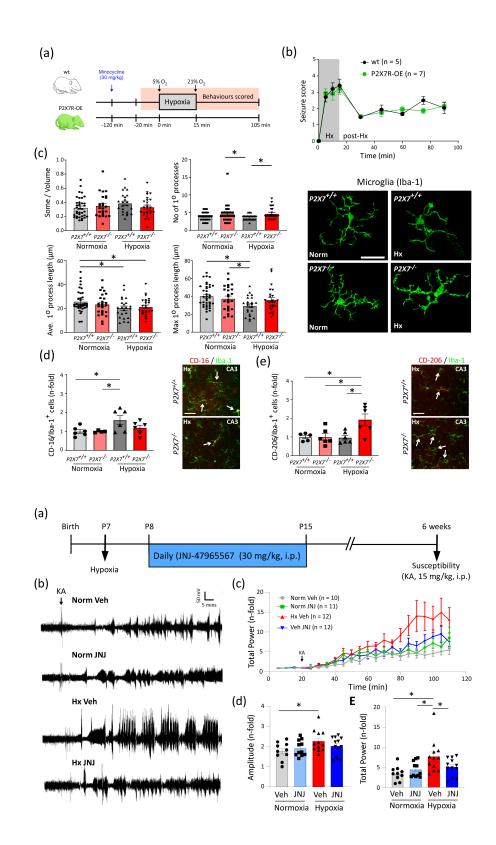
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Smith et al., manuscript submitted BJP amended.docx available at https://authorea.com/ users/512973/articles/589308-the-p2x7-receptor-contributes-to-seizures-and-inflammationdriven-long-lasting-brain-hyperexcitability-following-neonatal-hypoxia-in-mice

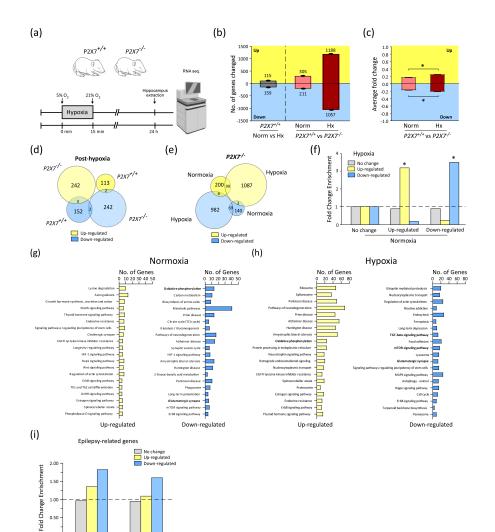












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Normoxia

Hypoxia