P2RY12 in traumatic brain injury: friend or foe according to sex?

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Background: Traumatic brain injury (TBI) triggers (1) neurovascular inflammation, (2) white matter injury (WMI) from demyelination, and (3) long-term behavioral deficits. Microglial activation and WMI can persist for years post-TBI. Microglia express purinergic receptors (P2Y) responsive to extracellular nucleotides. P2RY12, mainly found in microglia and platelets, is crucial for platelet aggregation and, more recently, shown to help perivascular microglia maintain blood–brain barrier (BBB) integrity. Sex-dependent P2RY12 expression patterns have also been reported. As TBI induces inflammation, BBB disruption, and gray/white matter damage—and since P2RY12 regulates microglia—we hypothesized a sex-dependent role of P2RY12 in these processes.

Materials and Methods: We assessed: (1) in vitro, the impact of myelin debris (from TBI mouse brains) on microglial activation under pro- and anti-inflammatory stimuli and the role of P2RY12; (2) in vivo, P2RY12 function in microglial activation, BBB permeability, and gray/white matter damage using a rodent TBI model in male and female P2RY12+/+ and P2RY12−/− mice, to identify sexual dimorphism.

Results: Myelin debris modulated anti-inflammatory microglial activation via P2RY12. In vivo, P2RY12 promoted anti-inflammatory activation 3 days post-TBI in males but reduced pro-inflammatory activation in females. Its effects on tissue outcomes also differed by sex: protective against brain lesions in males but not females; protective against white matter injury in females but not males; and variably affecting BBB disruption.

Conclusion: P2RY12 contributes to TBI outcomes in a sex-dependent manner. Next, we aim to identify which P2RY12-expressing cells (microglia and/or platelets) mediate these effects, with the goal of developing targeted therapeutic strategies for TBI.