p-267

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Regulation of extracellular progranulin in the brain

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State of the art: Loss-of-function mutations in progranulin (*GRN*) are a genetic cause of frontotemporal dementia. Progranulin is expressed by neurons and microglia in the brain, and is a secreted protein that is trafficked to lysosomes and maintains lysosomal function. Progranulin has anti-inflammatory and neurotrophic effects that may be mediated by extracellular progranulin, but little is known about the factors regulating extracellular progranulin levels in the brain.

Methodology: We used *in vivo* microdialysis to measure progranulin levels in interstitial fluid (ISF) of mouse medial prefrontal cortex (mPFC). Artificial cerebrospinal fluid (aCSF) containing 4% BSA was perfused through 2 mm polyethylene probes (1000 kDa cut-off) using a push-pull pump system (Atmos LM, Amuza). Progranulin levels were measured by ELISA (Adipogen).

Results: *Grn*–/– mice had no detectable ISF progranulin, and *Grn*+/– mice had approximately 50% lower ISF progranulin than wild-type. Cellular depolarization with KCl (100 mM) increased ISF progranulin, but stimulation of synaptic activity with picrotoxin (100 μM) or NMDA (50 μM) failed to increase ISF progranulin. In contrast, induction of systemic inflammation with LPS (10 mg/kg, i.p.) nearly doubled ISF progranulin levels after 8 hours. Ongoing studies are investigating the contribution of neurons and microglia to ISF progranulin using selective neuronal (*CamKII*-Cre:*Grnfl/fl*) and microglial (*Cx3Cr1*-Cre-ER:*Grnfl/fl*) progranulin knockout mice.

Conclusion: Our findings indicate that inflammation stimulates progranulin release in the mPFC, but that synaptic activity does not. Ongoing studies will clarify the contribution of neurons and microglia to ISF progranulin in the mPFC.

Conflicts of interest

No disclosures