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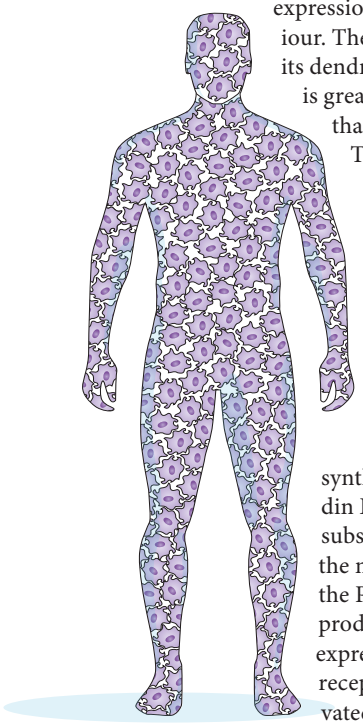
DEVELOPMENT

Microglia maketh the male

> microglial activation is required for the masculinization of the POA

Microglia are not only crucial in the response to neuronal damage — their role in the normal brain, including in brain development, is becoming increasingly evident. McCarthy and colleagues now add to the functional repertoire of microglia by showing that they are required for the masculinization of brain and behaviour in developing rats.

The preoptic area (POA) in the hypothalamus regulates the expression of sexual behaviour. The POA is larger and its dendritic spine density is greater in male rats than in female rats. This sexual differentiation depends on a perinatal surge in the production of testosterone, which is converted within the brain into oestradiol. A previous study showed that oestradiol upregulates the synthesis of prostaglandin E2 (PGE2), which subsequently regulates the masculinization of the POA. As microglia produce prostaglandins, express prostaglandin receptors and are activated during the critical period for sexual differentiation, the authors hypothesized a role for microglia in oestradiol-induced PGE2 production in the POA.



J.Vallis/NPG

The authors first showed that on postnatal day (PND) 2, the POA contained fewer total and activated microglia, with smaller cell bodies, in female rat pups than in males. Treating females with oestradiol on PND 0–1 increased these numbers to levels found in males, and this increase was prevented by co-treatment with minocycline (which inhibits microglial activation). Treatment with PGE2 on PND 0–1 also increased the number of activated microglia in the POA in females, whereas treating male pups with the cyclooxygenase (COX) inhibitor indomethacin (which inhibits prostaglandin production) had the opposite effect.

Female pups treated with oestradiol or with PGE2 on PND 0–1 also showed increased dendritic spine density in the POA compared with vehicle-treated females. The effects of both agents were prevented by co-treatment with the microglial inhibitor minocycline. Oestradiol also increased spine-like protrusions on cultured POA neurons from female pups but not in cultures from which microglia had been removed.

Together, these data show that oestrogen-induced PGE2 activates microglia, and this microglial activation is required for the masculinization of the POA. Next, the authors showed that microglia are also required for the oestrogen-induced stimulation of PGE2 synthesis. Specifically, female pups treated with oestradiol on PND 0–1 had higher PGE2 levels in the POA compared with vehicle-treated females, and co-treatment with minocycline prevented this effect.

The role of microglia in masculinization is also apparent on a behavioural level. Female rats treated with oestradiol after birth showed masculinized sexual behaviour in adulthood — particularly in terms of the number of mounts — and this was prevented when minocycline was co-administered with oestradiol.

Together, these findings support a model in which oestradiol induces the production of PGE2 — probably initially in neurons, as POA microglia did not express the α-form of oestrogen receptors — which in turn activates microglia and stimulates their own release of PGE2. This feed-forward loop of PGE2 production is required for the masculinization of the POA and therefore of sexual behaviour.

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ORIGINAL RESEARCH PAPER Lenz, K. M. *et al.* Microglia are essential to masculinization of brain and behavior. *J. Neurosci.* **33**, 2761–2772 (2013)