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Nramp1 is expressed in neurones and influences behavioural and neuroimmune stress responses
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**Abstract**

Polymorphisms in the human Natural Resistance Associated Macrophage Protein (*NRAMP1)* gene influence susceptibility to intracellular infections including tuberculosis. A naturally occurring mutation in the murine *Nramp1* gene has similar effects that are associated with impaired macrophage function. We studied the response to restraint stress in mice congenic for this infection-susceptible mutation. Infection-susceptible *Nramp1* mutant mice had an attenuated behavioural response to restraint and destroyed (by chewing) significantly smaller areas of the plastic tubes used to restrain them than the congenic infection-resistant mice that had the wild-type *Nramp1* gene.

Infection-susceptible *Nramp1* mice had larger adrenal glands and higher basal plasma corticosterone concentrations than infection-resistant mice. When subjected to restraint stress, infection-susceptible mice had attenuated hypothalamic stress responses (assessed by corticotrophin releasing factor mRNA by semi-quantitative *in situ* hybridisation) and depressed corticosterone responses (measured in plasma by radioimmunoassay). *Nramp1* therefore influenced the behavioural and neuroendocrine responses to stress in addition to the well-known effects of this gene on macrophage anti-microbial activity. Restraint stress prior to *Toxoplasma gondii* infection caused significantly increased mortality in *Nramp1* mutant but not wild type mice, suggesting that the neuroimmune functions of *Nramp1* contribute to its effects on infectious disease susceptibility and severity.

Nramp1 expression is generally restricted to macrophages but triple fluorescence immunochemical staining of cultured embryonic brain cells and adult brain sections revealed Nramp1 protein in late endosomes and lysosomes within neurones as well as microglia, potentially explaining our findings.

Nramp1 is therefore expressed in neurones and influences both behaviour and the neuro-immune response to stress.