MIS and its role in neuronal development

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Target tissues have a pivotal role in the regulation of neuronal cell number. However, the sizes of brain nuclei are also influenced by systemic factors that regulate body size, one of which is sex. Embryos are initially sexually indifferent, with the male phenotype being largely induced by androgens. However, few neurons express androgen receptors. The regression of the uterine anlagen in male embryos is induced by Mullerian Inhibitory Substance (MIS), which in the fetus is a male-specific hormone. We report here that the number of neurons in the lumbar lateral motor column of neonatal male mice is 15% greater than in female mice ($P=0.01$). The nuclei of male motoneurons are approximately 20% larger than their female counterparts ($p<0.001$). The survival and differentiation of motoneurons *in vitro* from E14-mice was promoted by physiological levels of MIS. Lastly, male mice with a null mutation of the type II MIS receptor have 18% fewer motor neurons than wild-type males ($P=0.01$) and the mean size of their motor neurons is 20% smaller ($p<0.001$). The number and size of motor neurons in the MISRII-/- males was not different to those of MISRII+/+ females. These results collectively implicate MIS as being responsible for producing a sexual dimorphism of the innervation of the hindlimb. MIS receptors were also detected in various other regions of the brain, which have no direct function in reproduction and in which sexual dimorphism has not previously been documented. The raises the issue of whether MIS has a broad role in creating gender-specific differences in the brain.