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Comparative effects of progesterone and the synthetic progestin norethindrone on neuroprotection in a model of spontaneous motoneuron degeneration

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Abstract

The Wobbler mouse has been proposed as an experimental model of the sporadic form of amyotrophic lateral sclerosis (ALS). The administration of natural progesterone (PROG) to Wobbler mice attenuates neuropathology, inhibits oxidative stress, enhances the expression of genes involved in motoneuron function, increases survival and restores axonal transport. However, current pharmacological treatments for ALS patients are still partially effective. This encouraged us to investigate if the synthetic progestin norethindrone (NOR), showing higher potency than PROG and used for birth control and hormone therapy might also afford neuroprotection. Two-month-old Wobbler mice (wr/wr) were left untreated or received either a 20 mg pellet of PROG or a 1 mg pellet of NOR for 18 days. Untreated control NFR/NFR mice (background strain for Wobbler) were also employed. Wobblers showed typical clinical and spinal cord abnormalities, while these abnormalities were normalized with PROG treatment. Surprisingly, we found that NOR did not increase immunoreactivity and gene expression for choline-acetyltransferase, drastically decreased GFAP + astrogliosis, favored proinflammatory mediators, promoted the inflammatory phenotype of IBA1+ microglia, increased the receptor for advanced glycation end products (RAGE) mRNA and protein expression and the activity of nitric oxide synthase (NOS)/NADPH diaphorase in the cervical spinal cord. Additionally, NOR treatment produced atrophy of the thymus. The combined negative effects of NOR on clinical assessments (forelimb atrophy and rotarod performance) suggest a detrimental effect on muscle trophism and motor function. These findings reinforce the evidence that the type of progestin used for contraception, endometriosis or replacement therapy, may condition the outcome of preclinical and clinical studies targeting neurodegenerative diseases.

Keywords: Amyotrophic lateral sclerosis; Motoneuron degeneration; Norethindrone; Progesterone; Synthetic progestin; Wobbler mouse.

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