

# Polydeoxyribonucleotide, an adenosine-A<sub>2A</sub> receptor agonist, preserves blood testis barrier from cadmium-induced injury via pERK 1/2/TGF-β3 signaling pathway

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Cadmium (Cd), a diffused environmental pollutant with adverse effects on male genital apparatus, impairs the blood-testis barrier (BTB) with consequent changes of its junctional complexes. Polydeoxyribonucleotide (PDRN), an adenosine A<sub>2A</sub> agonist extracted from trout sperm, has been shown to have positive effects on male reproductive system. We investigated the effects of PDRN on the morphological and functional changes induced *in vivo* by Cd in mice testes. Swiss mice were divided into four groups: control animals administered with 0.9% NaCl (1 ml/kg, i.p., daily); control animals administered with PDRN (8 mg/kg, i.p. daily), animals challenged with Cd chloride (CdCl<sub>2</sub>) (2 mg/kg i.p, daily) and animals challenged with CdCl<sub>2</sub>(2 mg/kg i.p., daily) and treated with PDRN (8 mg/kg i.p., daily). The experiments lasted 14 days. At the end of experiment, the testes were processed for biochemical, structural and ultrastructural evaluation. CdCl<sub>2</sub> increased the expression of pERK 1/2 and the levels of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH); it decreased testosterone (TE) and inhibin-B levels and induced structural damages in the extratubular compartment and in the seminiferous epithelium, which showed ultrastructural features of BTB disruption. Many TUNEL-positive germ cells were present, particularly in the peripheral parts of the tubules. CdCl<sub>2</sub> increased also tubular immunoreactivity of TGF-β3 and reduced claudin-11, occludin and N-cadherin immunoreactivity. PDRN administration reduced pERK 1/2 expression, FSH and LH levels; it increased TE and inhibin-B levels, ameliorated germinal epithelium changes, with mature spermatozoa and only some intercellular clefts, and protected BTB ultrastructure. Only few peripheral TUNEL-positive germ cells were present and the extratubular compartment was preserved, showing only a mild edema. Furthermore PDRN decreased TGF-β3 immunoreactivity and enhanced claudin-11, occludin and N-cadherin immunoreactivity. We demonstrate, for the first time, a protective effect of PDRN on Cd-induced damages of the BTB in mice testes. We suggest that the adenosine A<sub>2A</sub> agonist may play an important role against environmental Cd, and in particular against its harmful effects on gametogenesis.