Nucleoside triphosphate diphosphohydrolase-1 ectonucleotidase is required for normal vas deferens contraction and male fertility through maintaining P2X1 receptor function

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Résumé en anglais	In this work, we report that Entpd1(-/-) mice, deficient for the ectonucleotidase nucleoside triphosphate diphosphohydrolase-1 (NTPDase1), produce smaller litters (27% reduction) compared with wild-type C57BL6 animals. This deficit is linked to reduced in vivo oocyte fertilization by Entpd1(-/-) males (61 +/- 11% versus 88 +/- 7% for Entpd1(+/+)). Normal epididymal sperm count, spermatozoa morphology, capacitation, and motility and reduced ejaculated sperm number (2.4 +/- 0.5 versus 3.7 +/- 0.4 million for Entpd1(+/+)) pointed to vas deferens dysfunction. NTPDase1 was localized by immunofluorescence in the tunica muscularis of the vas deferens. Its absence resulted in a major ATP hydrolysis deficiency, as observed in situ by histochemistry and in primary smooth muscle cell cultures. In vitro, Entpd1(-/-) vas deferens displayed an exacerbated contraction to ATP, a diminished response to its non-hydrolysable analog alphabetaMeATP, and a reduced contraction to electrical field stimulation, suggesting altered P2X1 receptor function with a propensity to desensitize. This functional alteration was accompanied by a 3-fold decrease in P2X1 protein expression in Entpd1(-/-) vas deferens with no variation in mRNA levels. Accordingly, exogenous nucleotidase activity was required to fully preserve P2X1 receptor activation by ATP in vitro. Our study demonstrates that NTPDase1 is required to maintain normal P2X1 receptor functionality in the vas deferens and that its absence leads to impaired peristalsis, reduced spermatozoa concentration in the semen, and, eventually, reduced fertility. This suggests that alteration of NTPDase1 activity affects ejaculation efficacy and male fertility. This work may contribute to unveil a cause of infertility and open new therapeutic potentials.
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