A Drosophila Model for the Functional Analysis of Human Androgen Receptor with a Polyglutamine Stretch Amplification

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Expansion of a polyglutamine tract at the N-terminus of the human androgen receptor (hAR) causes spinal and bulbar muscular atrophy (SBMA), an X-linked motor neuronopathy. This disorder affects lower motor and sensory neurons with relative sparing of other brain structures. In cell culture experiments, we detected a delayed cytoplasmic-nuclear translocation of hAR with a polyglutamine stretch of 77 (hARQ77) compared with a wild-type receptor carrying a stretch of 22 glutamine residues (hARQ22). To investigate whether the cellular localization of the mutant hAR contributes to the SBMA, we generated transgenic *Drosophila* carrying hARQ22 and hARQ77 with or without a nuclear localisation signal (NLS) (hARΔNLSQ22 & hARΔNLSQ77). The latter constructs are predominantly cytoplasmic since they lack the NLS that is needed for the nuclear transport of the hAR. The receptor constructs were targeted to distinct tissues of the fly using the Gal4-UAS system. Transgenic flies with targeted expression of the AR in the eye induced by a glass multimer reporter (*gmr*) promoter were analyzed in the absence and presence of the androgen dihydrotestosterone (DHT) and other ligands. Flies expressing the hARQ77 protein but not the hARQ22 showed severely disrupted eye morphology and depigmentation. In contrast, flies expressing hARΔNLSQ77 only showed mild eye phenotype. In both cases, the eye defects were greatly aggravated by DHT treatment. Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assay showed that the defects correlated with the presence of apoptotic cells in the eye. Antiandrogens and other steroids suppressed the eye defects. These results together demonstrate that nuclear rather than cytoplasmic localization of the hAR with amplified polyglutamine stretch contributes more efficiently to the optical degeneration. Additionally our results suggest potential therapeutic advantages of antiandrogens and other ligands in the clinical management of SBMA.