Progress in Neurobiology 99 (2012) 257–261

Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Developing treatment for spinal and bulbar muscular atrophy

Kenneth H. Fischbeck *

Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 35-2A1000, 35 Convent Dr., Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 13 February 2012
Received in revised form 14 May 2012
Accepted 15 May 2012
Available online 2 June 2012

Keywords:
Spinal and bulbar muscular atrophy
Kennedy's disease
Motor neuron disease
Androgen receptor
Polyglutamine disease
IGF-1

ABSTRACT

Spinal and bulbar muscular atrophy is unique among the polyglutamine diseases in that the toxicity of the mutant protein, the androgen receptor, is ligand-dependent. In cell culture and animal models the mutant androgen receptor causes protein aggregation and alterations in transcriptional regulation, axonal transport, and mitochondrial function. Various therapeutic approaches have shown efficacy in mouse models, including androgen reduction and agents that alter the processing and degradation of the mutant androgen receptor protein, such as HSP90 inhibitors, IGF-1, and ASC-J9. Clinical trials of androgen-reducing agents have shown indications of efficacy but not proof of clinically meaningful benefit to date. This trial experience has set the stage for future clinical studies of other agents that have been found to be beneficial in transgenic animal models.

Published by Elsevier Ltd.

Contents

1. Introduction

Spinal and bulbar muscular atrophy (SBMA, Kennedy's disease) is an X-linked, adult-onset disease with slowly progressive weakness of the bulbar and extremity muscles due to degeneration of motor neurons in the brainstem and spinal cord. Affected males may show signs of androgen insensitivity, such as breast enlargement and reduced fertility. The causative mutation is a CAG repeat expansion in the androgen receptor gene that leads to an expanded polyglutamine tract in the N-terminal domain of the receptor protein (La Spada et al., 1991). SBMA is thus one of about 30 diseases known to be caused by repeat expansion and one of at least nine that are caused by expanded polyglutamine tracts. This review summarizes what has been learned since the disease gene discovery about the pathophysiology of SBMA and the prospects for treatment. Other reviews have recently appeared elsewhere (Parodi and Pennuto, 2011; Banno et al., 2012)

The androgen receptor is a nuclear receptor, and the N-terminal domain is in a part of the protein separate from the hormone and DNA binding domains, a part of the protein that is involved in interaction with other nuclear proteins. Thus the mutant receptor has normal ligand biding, and in the presence of ligand it dissociates from cytoplasmic heat shock proteins and is normally taken up into the nucleus, but target gene activation is altered due to aberrant binding to other nuclear factors. This causes some loss of normal receptor function, as evidenced by functional studies and by the signs of androgen insensitivity that occur in patients with

Abbreviations: AR, androgen receptor; HDAC, histone deacetylase; IGF-1, insulin-like growth factor 1; PI3K, phosphatidylinositol 3 kinase; SBMA, spinal and bulbar muscular atrophy; QMA, quantitative muscle assessment.

* Tel.: +1 301 435 9318; fax: +1 301 480 3365.
E-mail address: kf@ninds.nih.gov.

0301-0082/$ – see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.pneurobio.2012.05.012

SBMA, but the primary effect is to cause a toxic gain of function in the receptor protein, i.e., it alters the protein so that it becomes toxic to motor neurons. This is based on the finding that animals and humans with other mutations that cause a loss of androgen receptor function have a different phenotype, with feminization but not the progressive weakness and motor neuron loss of SBMA. Further support for a gain of function comes from the finding that the mutant protein is toxic and reproduces features of the disease phenotype when introduced into cultured cells and transgenic animals. In these model systems, the toxicity is associated with aggregation of the mutant protein, and it is ligand (androgen) dependent.

2. SBMA disease mechanism

As with other polyglutamine diseases, the mutant androgen receptor is prone to aggregation and forms inclusions in patient tissues and in cell culture and animal models. In cell culture models, there is repeat-dependent cell death that is greater with nuclear localization. The toxicity is associated with transcriptional dysregulation, aberrant interaction with other nuclear factors, and changes in histone acetylation (Shimohata et al., 2000; McCampbell et al., 2000, 2001; Lieberman et al., 2002; Taylor and Fischbeck, 2002).

Importantly, the toxicity of the mutant protein is ligand-dependent in transgenic flies and mice. In flies, which do not have endogenous androgens, the mutant gene has no effect unless they are exposed to androgens in their food (Takeyama et al., 2002; Pandey et al., 2007). And in transgenic mice, where the mutant human gene is no longer on the X chromosome, the disease manifestations are still only seen in males. Castration of the males rescues the phenotype, and females given exogenous androgens develop disease manifestations (Katsuno et al., 2002; Chevalier-Larsen et al., 2004). Thus it appears that SBMA occurs in males rather than females because they have higher androgen levels, and the disease is male-limited rather than simply X-linked recessive. A report of one family with homozygous females who are more mildly affected than their male relatives indicates that the disease is androgen dependent in humans, as it is in transgenic animals (Schmidt et al., 2002). Cell culture models of ligand-dependent toxicity are also available (Palazzolo et al., 2007; Montie et al., 2011), and these can be used to identify potential therapeutic targets.

Recent evidence indicates that native functions and interactions of the receptor protein are important to its toxicity. When events downstream of ligand-dependent androgen receptor activation were systematically evaluated in mouse and fly models of SBMA, it was found that nuclear translocation of the mutant protein is necessary but not sufficient for its toxicity and that DNA binding may be necessary (Montie et al., 2009; Nedelsky et al., 2010). Mutagenesis studies demonstrated that a functional AF-2 domain is essential for toxicity, a finding corroborated by a genetic screen that identified AF-2 interactors as dominant modifiers of degeneration. These findings indicate that SBMA pathogenesis is mediated by misappropriation of native protein function, a mechanism that may be applicable to other polyglutamine diseases.

3. Clinical trials of androgen reduction

Anti-androgen therapy is very effective at blocking the disease onset and preventing the motor deficit in the transgenic mice (Katsuno et al., 2003). This raises the question of whether or not such treatment is effective in SBMA patients.

3.1. Leuprorelin

Randomized, placebo-controlled clinical trials in Japan with the centrally acting androgen-reducing agent leuprorelin in SBMA did not show significant effects on overall muscle strength and function, although there were indications of beneficial effects on swallow function. First, a phase 2 study in 50 subjects showed decreased nuclear accumulation of the mutant androgen receptor in scrotal skin cells and improved swallowing time on cine-swallow studies after 48 weeks (Banno et al., 2009). Later, a phase 3 study of the same duration in nearly 200 subjects showed no effect on swallow function overall, but there was a significant beneficial effect in a subgroup with disease duration less than 10 years (Katsuno et al., 2010).

3.2. Dutasteride

A randomized, controlled trial was also recently performed at the National Institutes of Health. This study used a different androgen-reducing agent, dutasteride, which blocks the conversion of testosterone to the more potent dihydrotestosterone by 5-alpha reductase. The rationale was that this agent would block toxic effects of dihydrotestosterone in motor neurons, where 5-alpha reductase is highly expressed (Pozzi et al., 2003), while preserving the anabolic effects of testosterone in muscle. A baseline cross-sectional analysis of clinical history, laboratory findings, and muscle strength and function was done in 57 patients with genetically confirmed disease who were recruited for the trial (Rhodes et al., 2009). There was an average delay of over 5 years from onset of weakness to diagnosis in this cohort. Muscle strength and function correlated directly with serum testosterone levels and inversely with CAG repeat length, age, and duration of weakness. Motor unit number estimation was decreased by about half compared to healthy controls (Lehky et al., 2009). Sensory nerve action potentials were reduced in nearly all subjects. The direct correlation of testosterone levels with muscle strength indicates that androgens may have a positive effect on muscle function in SBMA patients, in addition to the toxic effects described in animal models (Rhodes et al., 2009).

A randomized, double-blind, placebo-controlled, single-site clinical trial was then done (Fernández-Rhodes et al., 2011). Participants were randomly assigned to receive dutasteride or placebo orally for 24 months. The subjects and investigators were masked to treatment allocation. The primary outcome measure was quantitative muscle assessment (QMA). At 24 months, the placebo group showed a decrease of 4.5% from baseline in weight-scaled muscle strength as indicated by QMA, and the dutasteride group had an increase in strength of 1.3%, but this difference between the groups was not significant. Quality of life, as measured by the physical component summary of the SF-36v2 questionnaire, favored dutasteride ($p = 0.01$), whereas the mental component summary favored placebo (Fig. 1). With dutasteride, the subjects felt physically better but mentally worse, perhaps due to decreased libido with androgen reduction. Individual sub-scales within these component summaries did not show significant change, however. The dutasteride group had fewer patients reporting falls than did the placebo group; there were no other significant differences in reported adverse events. Although this study did not show a significant effect of dutasteride on the progression of muscle weakness in SBMA, there were secondary indications of positive effects compared with placebo.

Translating a therapeutic intervention that is effective in pre-clinical mouse studies into effective treatment in patients is challenging, in part because the patient population is more diverse and the clinical manifestations are more variable and more slowly progressive. A longer trial duration or larger number of patients and better outcome measures may be needed to show an effect on disease progression. This study identified performance testing and quality of life measures as potentially useful endpoints for future therapeutic trials, but more needs to be done to promote early