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Spinal and Bulbar Muscular Atrophy Overview

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Abstract

Spinal and bulbar muscular atrophy is an X-linked neuromuscular disease caused by an expanded repeat in the androgen receptor gene. The mutant protein is toxic to motor neurons and muscle. The toxicity is ligand-dependent and likely involves aberrant interaction of the mutant androgen receptor with other nuclear factors leading to transcriptional dysregulation. Various therapeutic strategies have been effective in transgenic animal models, and the challenge now is to translate these strategies into safe and effective treatment in patients.

Keywords

Androgen receptor; Polyglutamine; Spinal and bulbar muscular atrophy

Spinal and bulbar muscular atrophy (SBMA, Kennedy's disease) is a progressive X-linked neuromuscular disease characterized by bulbar and extremity muscle weakness, atrophy, and fasciculations. Affected males may also show signs of androgen insensitivity, such as breast enlargement and reduced fertility. SBMA is caused by expansion of a CAG repeat in the androgen receptor gene at Xq11-q12 (La Spada et al. 1991). This was the first repeat expansion mutation to be discovered.

The androgen receptor is a member of the steroid and thyroid hormone receptor family, and like the other family members it is an intracellular receptor. In the absence of ligand it is located in the cytoplasm in a complex with heat shock proteins. In the presence of ligand, testosterone or dihydrotestosterone, the receptor dissociates from the heat shock protein complex and is actively taken up into the nucleus, where it interacts with other nuclear proteins and binds as a dimer to recognition sequences in the DNA of target genes throughout the genome. The androgen receptor thus functions as a ligand-activated transcription factor that alters target gene expression. The expanded repeat is in the androgen receptor gene's first exon, which encodes the N-terminal transactivation domain, a part of the protein separate from the DNA and hormone-binding domains (Fig. 1). The CAG repeat is in a translated portion of the gene and in a reading frame to encode a polyglutamine tract near the amino terminal of the protein. The tract is variable, ranging in length from about 13 to 30 glutamines in normal individuals. In SBMA patients, it is two to three times its normal length, and the repeat length correlates with disease severity: the longer the repeat, the

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earlier the onset and the more severe the disease manifestations. As with other repeat expansion diseases, the expanded repeat in SBMA is unstable and shifts in length as it is passed from one generation to the next.

The polyglutamine expansion causes both a loss and gain of androgen receptor function (Fig. 2). The loss of function is evident in the clinical manifestations of the disease (breast enlargement and reduced fertility), and since androgens are trophic for motor neurons and anabolic in muscle the loss may be contributing to motor neuron and muscle degeneration. However, the main effect of the polyglutamine expansion is a toxic gain of function in the receptor protein. We know this because other mutations that cause loss of androgen receptor function have a different phenotype, androgen insensitivity syndrome, with feminization but not the progressive weakness of SBMA. Thus the repeat expansion has the effect of making the receptor toxic to motor neurons and muscle.

The toxicity of the mutant protein is seen in cell culture and transgenic animal models, where the mutant androgen receptor accumulates in inclusions (which may represent a cellular protective response) and has a tendency to aggregate with increasing repeat length. In cell culture, the toxicity is repeat length-dependent and greater with nuclear localization. The mutant protein has aberrant interactions with other nuclear factors, leading to altered histone acetylation and transcriptional dysregulation. This in turn leads to adverse effects on axonal transport, signal transduction, and mitochondrial function, resulting in dysfunction and death of motor neurons and muscle degeneration. Recent evidence has implicated altered autophagy in SBMA. Histone deacetylase 6 (HDAC6) was found to play an important role in protein degradation via autophagy in an SBMA fly model (Pandey et al. 2007), and HDAC6 has also been found to be decreased in SBMA-induced pluripotent (iPS) cells (Grunseich et al. 2014a). Altered regulation of autophagy by p62 and TFEB has been found in SBMA cell culture and mouse models (Doi et al. 2013; Chua et al. 2014; Cortes et al. 2014a).

The toxicity of the mutant androgen receptor is ligand-dependent (i.e., dependent on androgens) in transgenic flies and mice. In flies, which have no endogenous androgen, transgenic mutant androgen receptor results in a degenerative phenotype only when the animals are exposed to androgens in their feed (Pandey et al. 2007). And in transgenic mice with autosomal insertion of the mutant gene, only males, which have higher androgen levels than females, have full disease manifestations. Females given androgens develop motor findings, and castration or pharmacological anti-androgen treatment (leuprorelin) blocks the disease onset and prevents the motor deficit (Chevalier-Larsen et al. 2004; Katsuno et al. 2003). This raises the question of whether androgen reduction may be similarly effective in patients with SBMA.

Over the past several years, three randomized, placebo-controlled clinical trials have tested androgen reduction treatment in SBMA. First, a 50-subject trial of leuprorelin vs. placebo for 48 weeks showed no effect on the primary outcome measure of muscle function (Amyotrophic Lateral Sclerosis Functional Rating Scale, ALSFRS), although there was a secondary effect on swallowing (Banno et al. 2009). Later, a 200-subject leuprorelin trial found no effect on a primary measure of swallowing, except in subjects less than 10 years

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from onset on post hoc analysis (Katsuno et al. 2010). Subsequently, a 50-subject trial of a different androgen-reducing agent, dutasteride, for 2 years found no effect on the primary measure of muscle strength (Quantitative Muscle Assessment, QMA), but secondary effects on physical quality of life (Fernandez-Rhodes et al. 2011). Overall, these studies do not support the use of androgen-reducing therapy in SBMA (Fischbeck 2013).

Recently, two SBMA patients with unusual presentations have brought further insight into the disease mechanism and prospects for treatment. First, a patient with a 68 CAG repeat, the longest reported in SBMA, had abnormal genital development in addition to other manifestations of the disease, indicating that loss of androgen receptor function during development may be a part of the clinical phenotype (Grunseich et al. 2014b). And second, a transgender patient with SBMA had typical disease manifestations after 15 years of fully feminizing androgen reduction starting before the onset of muscle weakness, indicating that androgen reduction alone may not be enough to block the disease even when started early and continued for an extended period (Lanman et al., unpublished).

Based on the clinical trial experience, SBMA presents several challenges for therapeutics development: (1) slow disease progression, thus a need for treatment that improves function rather than slows progression; (2) a need for treatment to start early; (3) a need for reliable clinical outcome measures and markers to show biological effects of treatment; and (4) a need for better therapeutic targets. Therapeutic targets for SBMA include steps along the pathogenic path that can be inhibited and protective mechanisms that can be enhanced. Our current understanding of the pathogenesis is that the mutant protein becomes toxic in the presence of ligand and is taken up into the nucleus where it is prone to aggregation and has aberrant interactions with other nuclear factors that lead to transcriptional dysregulation and disrupt signal transduction, transport mechanisms, and mitochondrial function. Protective mechanisms include the heat shock response, the ubiquitin-proteasome pathway, and autophagy. Thus, a number of targets have been identified where engagement in transgenic mice is efficacious, including (1) enhancing the heat shock response through HSP90 inhibition, e.g., with the geldanamycin derivatives 17-AAG and 17-DMAG (Waza et al. 2005; Tokui et al. 2009), (2) enhancing androgen receptor degradation and activating protective pathways with curcumin derivatives ASC-J9 and ASC-JM17 (Yang et al. 2007; Bott et al., unpublished), (3) inhibition of CGRP-JNK signaling with naratriptan (Minamiyama et al. 2012), and (4) rescue of mitochondrial function through PPARγ with pioglitazone (Iida et al. 2015).

Probably the best therapeutic target is the mutant protein itself, since reducing levels of the protein or blocking its toxicity would prevent all the downstream deleterious effects. Approaches that have recently been reported to be effective in transgenic mice include decreasing disease gene expression and altering post-translational modification of the protein to reduce its toxicity. Phosphorylation of the mutant androgen receptor by Akt blocks its toxicity by inhibiting ligand binding and enhancing degradation of the protein (Palazzolo et al. 2007), and activation of Akt by IGF-1 through PI3K mitigates disease manifestations in transgenic mice, either with transgenic overexpression of IGF-1 in muscle or with administration of stabilized IGF-1 after the onset of disease manifestations (Palazzolo et al. 2009; Rinaldi et al. 2012).

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An alternative to drug therapy is exercise. Exercise has been beneficial in mouse and human studies of amyotrophic lateral sclerosis, spinal muscular atrophy, and sarcopenia, and it has been reported to increase serum IGF-1. In a recent clinical exercise trial at the National Institutes of Health, 50 SBMA subjects were randomized to functional exercise or stretching for 12 weeks (Shrader et al. 2015). Blinded evaluation was done at baseline and at the end of the study. Compliance was encouraged by exercise partners, phone contact, home videos, and accelerometry. Outcome measures were muscle function, quality of life, adverse events, and IGF-1. There was no significant difference in muscle function overall, but most low-functioning patients improved. There was no change in IGF-1.

There are several criteria to be met in deciding whether to take a therapeutic approach into a proof-of-concept clinical trial in patients: (1) unmet medical need; (2) a strong rationale for the therapeutic approach, with supportive animal studies; (3) a favorable risk: benefit ratio; (3) adequate measures to confirm that the drug has the desired biological effect; and (4) clinical trial readiness, with patient availability and reliable clinical outcome measures. All of these criteria now apply to SBMA, and such a trial is currently underway at the National Institutes of Health and other sites with Novartis agent BVS857 (ClinicalTrials.gov identifier NCT02024932). The trial includes safety measures, biological measures including thigh muscle volume by MRI and muscle histology, and clinical efficacy measures including muscle function and physical quality of life. The trial is designed as a two-part study, with dose escalation, safety, and muscle biopsies for biomarkers in the first part, followed by a 12-week controlled efficacy trial.

Finally, therapeutic strategies to reduce disease gene expression with miRNA and oligonucleotides have had promising pre-clinical results and are approaching clinical application. The mutant transcript can be reduced indirectly by depleting the RNA-binding protein CELF2 (Miyazaki et al. 2012) or directly with miRNA targeting the androgen receptor mRNA itself (Pourshafie et al., unpublished). Oligonucleotide therapy has been in clinical trials for other neuromuscular diseases including Duchenne muscular dystrophy, familial amyotrophic lateral sclerosis, and spinal muscular atrophy, and mouse studies indicate that systemic delivery may be effective in SBMA (Cortes et al. 2014b; Lieberman et al. 2014; Rinaldi et al. 2014). Recent findings in a different SBMA mouse model indicate that CNS delivery may also be effective (Sahashi et al. 2015).

In conclusion, insights gained into the pathophysiology of SBMA since the causative mutation was identified in 1991 have led to a number of therapeutic strategies with efficacy in transgenic mouse models. The challenge now is to convert the mouse results into effective treatment in patients. While there is still much work to be done, the goal of safe and effective therapy for SBMA is now clearly in view.

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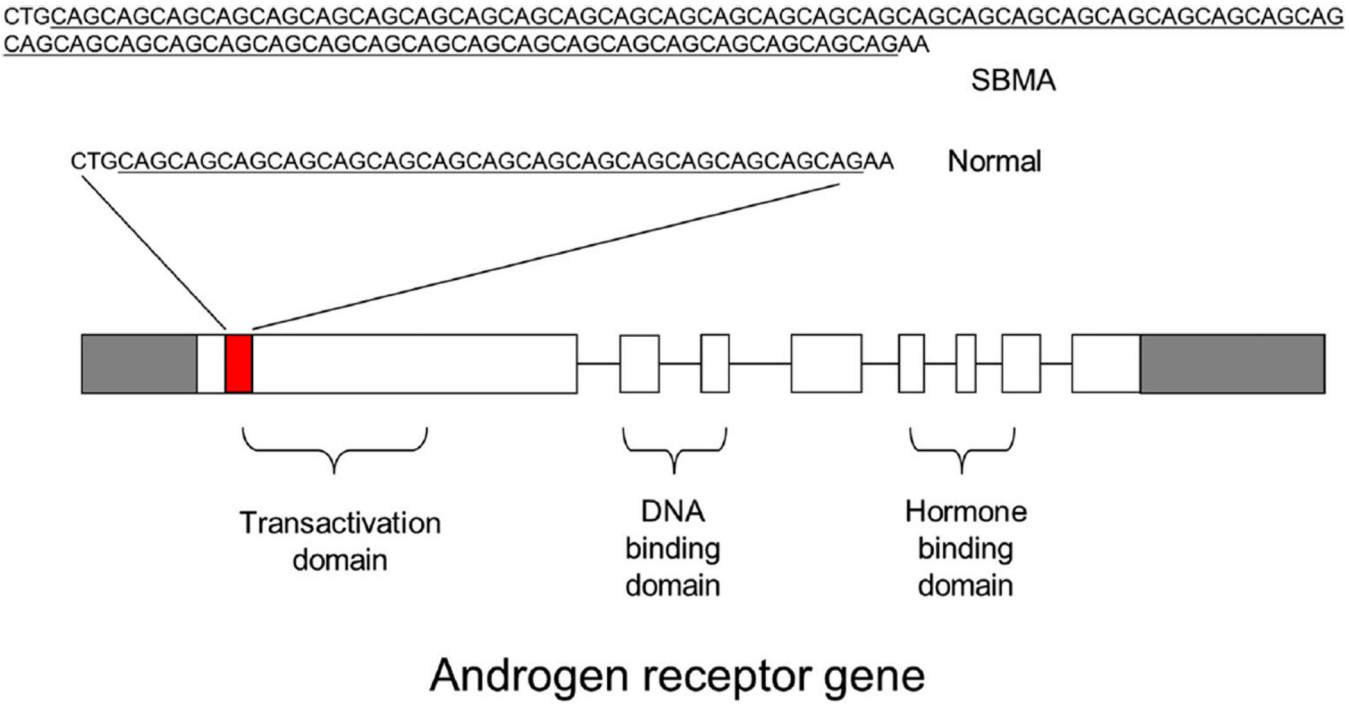
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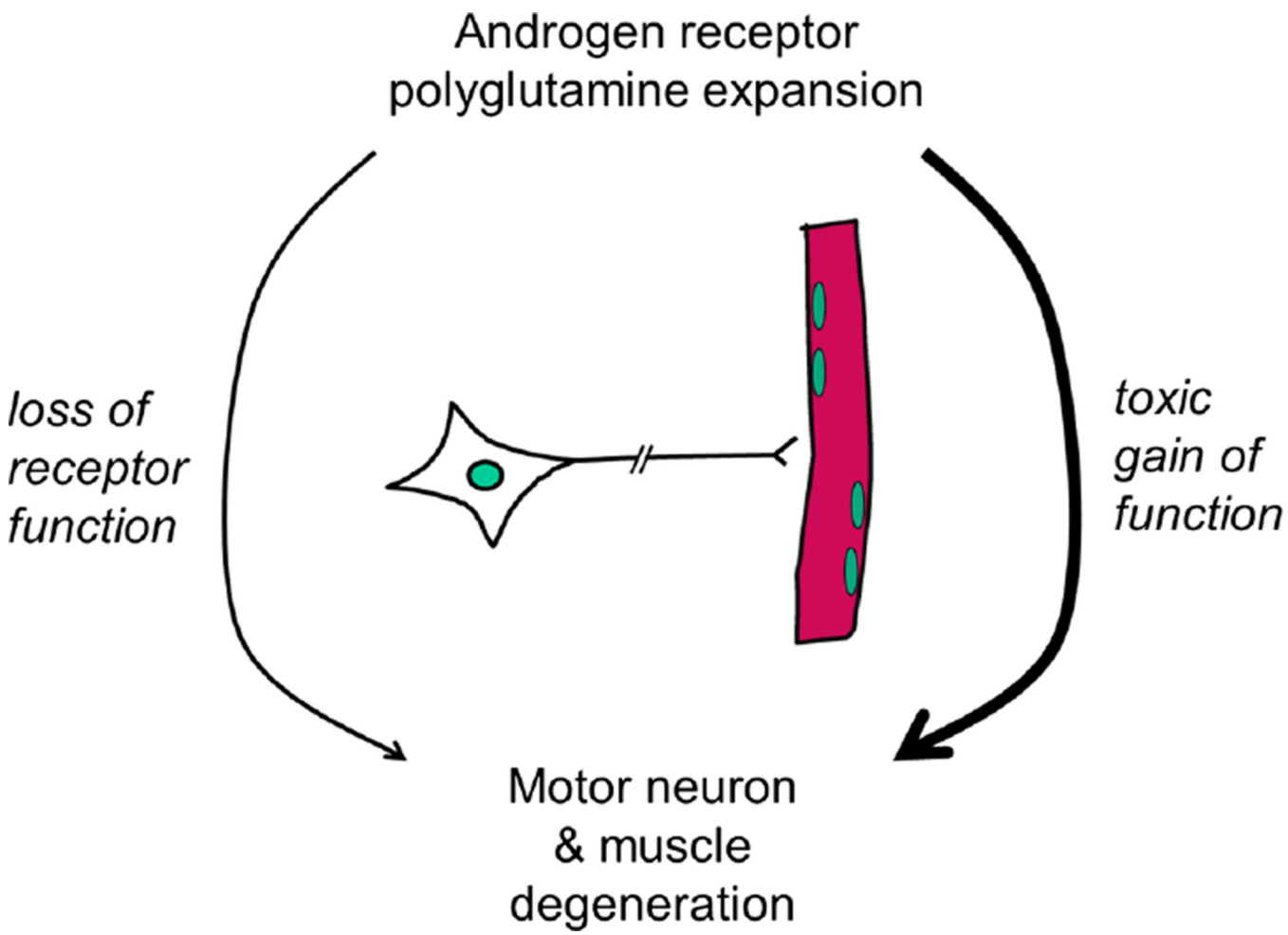

Fig. 2.

The mutant androgen receptor protein causes degeneration of motor neurons and muscle through a toxic gain of function mechanism