News Release

Restoring early postnatal synaptic dysregulation rescues motor neuron degeneration in a mouse model of Spinal and Bulbar Muscular Atrophy

Key Points

- **Motor neurons exhibit hyperexcitability due to the increased expression of excitatory synaptic genes during the early postnatal stage in a mouse model of spinal and bulbar muscular atrophy (SBMA), an adult-onset hereditary neurodegenerative disease.**
- **iPSC-derived motor neurons from SBMA patients also exhibit neuronal hyperexcitability.**
- **Suppression of early postnatal hyperexcitability using nucleic acid therapeutics ameliorates motor neuron degeneration in adulthood.**

Summary

A research group led by Designated Assistant Prof. Tomoki Hirunagi and Prof. Masahisa Katsuno from the Department of Neurology, Nagoya University Graduate School of Medicine, in collaboration with Prof. Yohei Okada from the Department of Neural iPSC Research, Institute for Medical Science of Aging, Aichi Medical University, revealed the ultra-early pathology of spinal and bulbar muscular atrophy (SBMA), a hereditary neurodegenerative disease. This work was published online in *Nature Communications* on March 27, 2026.

SBMA is a male-specific neurological disease caused by pathogenic variants in the androgen receptor (*AR*) gene, leading to progressive skeletal muscle atrophy and weakness beginning in midlife. Mutant AR protein forms aggregates within the nuclei of motor neurons that control muscle movement. However, the timing and mechanisms of the neurotoxicity caused by the mutant AR protein have remained unclear.

This study revealed that in SBMA model mice, excitatory synapse gene expression increases immediately after birth, placing motor neurons in a state of hyperexcitability. Similar changes were also observed in induced-pluripotent stem cell (iPSC)-derived motor neurons derived from SBMA patients. Furthermore, nucleic acid therapeutics that reduced mutant AR levels or suppressed the expression of excitatory synaptic genes during the early postnatal period improved motor function and ameliorated motor neuron degeneration in SBMA mice. These results suggest that very early intervention holds therapeutic potential for modifying disease progression in SBMA.

Research Background

Neurodegenerative diseases are a group of intractable neurological disorders characterized by the accumulation of abnormal protein aggregates in neurons of the brain and spinal cord, leading to impairments in motor and cognitive functions. While these symptoms typically emerge in middle age or later, it is well established that the accumulation of abnormal proteins begins decades before symptom onset, indicating the presence a prolonged asymptomatic period. However, the specific abnormalities that occur during this preclinical phase remain poorly understood (Fig. 1).

This study investigated abnormalities that occur at the very early stage of spinal and bulbar muscular atrophy (SBMA) using a mouse model of SBMA and induced pluripotent stem cell (iPSC)-derived motor neurons from SBMA patients. SBMA is a neuromuscular disorder characterized by atrophy and progressive muscle weakness of the facial, bulbar, and limb muscles, and it predominantly affects males. Leuprorelin acetate, which suppresses the production of the male hormone testosterone, has been approved in Japan as a treatment for SBMA. SBMA is caused by an abnormal expansion of CAG repeats in the androgen receptor (AR) gene, resulting in an expanded polyglutamine tract in the AR protein. Upon binding to testosterone, mutant AR protein translocates to the nucleus, leading to toxicity in motor neurons.

In this study, we focused on the period known as the testosterone surge, during which testosterone levels transiently increase immediately after birth, and investigated alterations in motor neurons at the very early stage of SBMA. Furthermore, we examined whether iPSC-derived motor neurons from SBMA patients exhibit changes similar to those observed in the SBMA mouse model, and evaluated the potential of early therapeutic intervention using nucleic acid therapeutics.

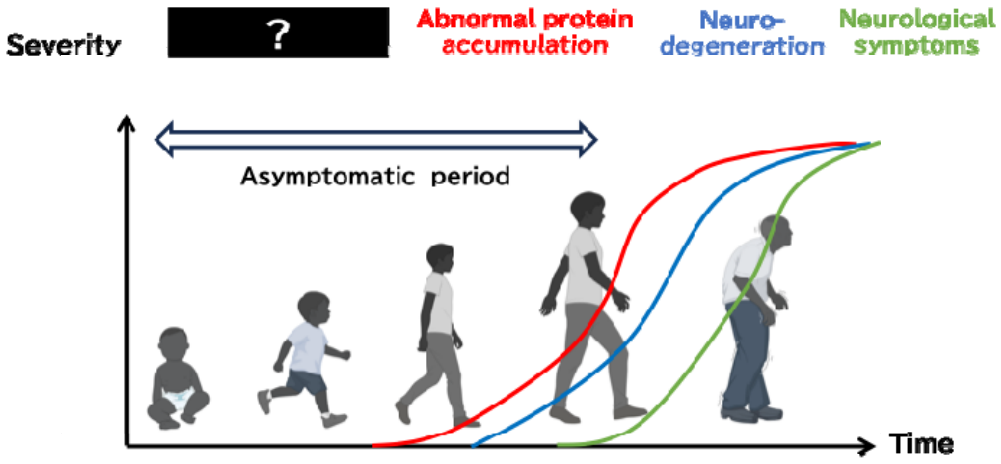

Fig. 1. Time course of neurodegenerative disease
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Research Results

In this study, we first analyzed the subcellular localization of mutant AR protein in motor neurons of neonatal SBMA mice. The results showed that mutant AR accumulated in the nuclei of motor neurons in male mice, but not in female mice, at postnatal day 1 (P1). Administration of testosterone to female mice at P1 induced nuclear accumulation of mutant AR by P4, demonstrating that neonatal testosterone exposure influences the subcellular localization of the mutant AR (Fig. 2).

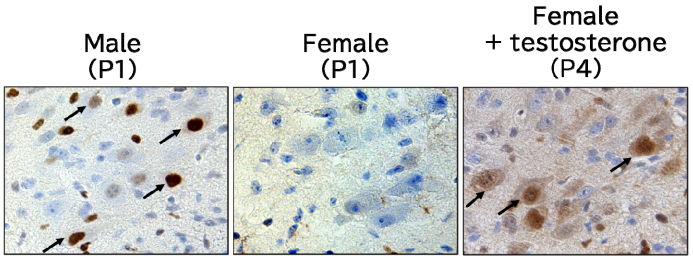

Fig. 2. Localization of mutant AR in motor neurons of SBMA mice at early postnatal periods.
Arrows indicate nuclear accumulation of mutant AR.
P1 and P4 means postnatal day 1 and 4, respectively.

Next, to verify the toxicity of the mutant AR in motor neurons during the early postnatal period, we administered an antisense oligonucleotide targeting mutant AR (AR-ASO) into the cerebral ventricles of SBMA mice at P1. Although the effect of AR-ASO diminished approximately two weeks after administration, this treatment improved survival and motor performance in the rotarod test and mitigated motor neuron degeneration at 13 weeks of age (Figure 3). These results indicate that mutant AR toxicity at the very early stage influences subsequent motor neuron degeneration at later stages.

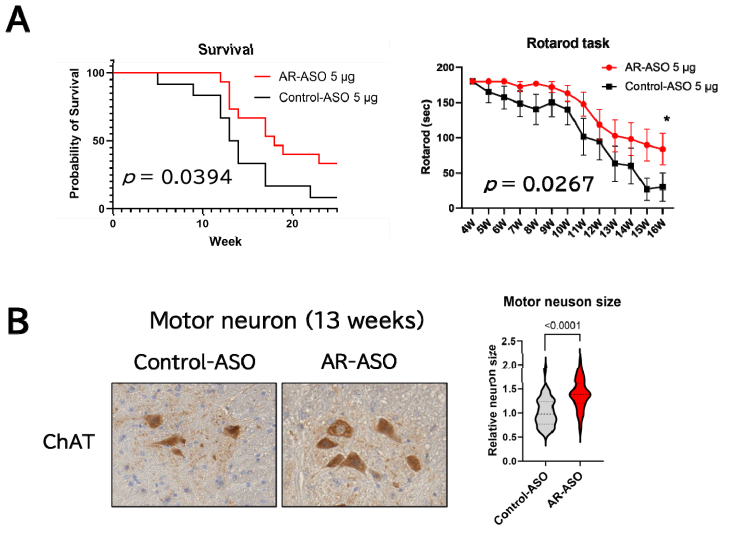

Fig. 3. Effects of Neonatal Treatment with AR-ASO
(A) Administration of AR-ASO on postnatal day 1 extends survival and improves motor function in SBMA mice.
(B) AR-ASO attenuates motor neuron degeneration of SMBA mice at 13 weeks of age. ChAT: a marker for motor neurons.

To investigate molecular changes in motor neurons at the very early stage of SBMA, we performed comprehensive gene expression analysis using RNA sequencing (RNA-seq). The results showed that the expression of genes related to excitatory synapses, which enhance neuronal activity, was elevated in SBMA mice compared with wild-type mice at P7 (Fig. 4A). Furthermore, neonatal suppression of the mutant AR using AR-ASO mitigated these increases. The expression of excitatory synaptic genes was also elevated in iPSC-derived motor neurons from patients with SBMA (Fig. 4A). To assess motor neuron excitability, we evaluated neuronal activity using calcium imaging. This analysis revealed that iPSC-derived motor neurons from SBMA patients exhibited increased firing intensity and burst frequency compared with those from healthy controls, indicating a state of hyperexcitability (Fig. 4B).

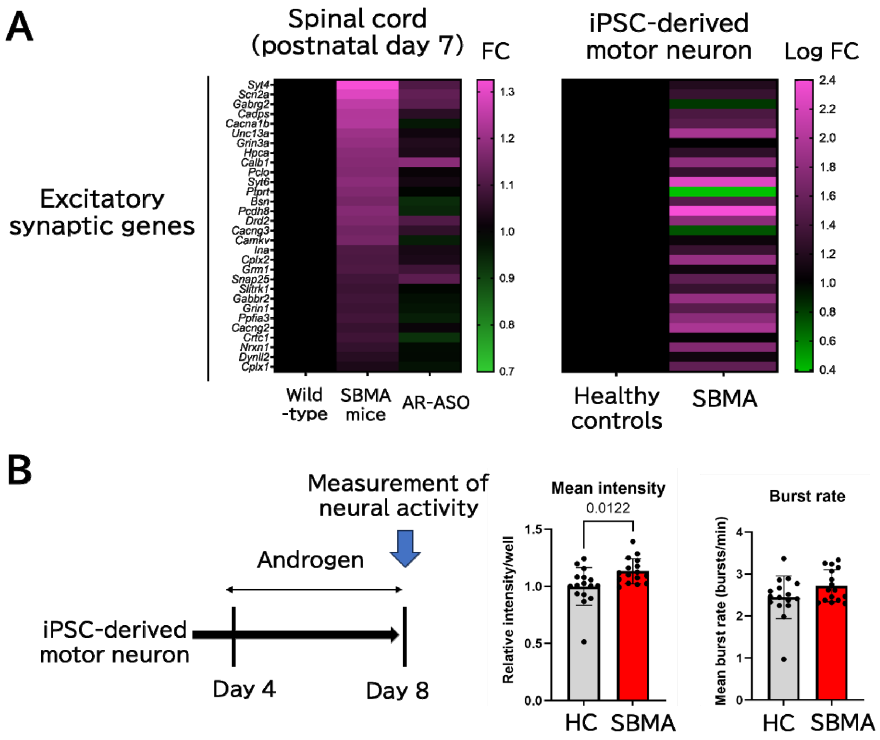

Fig. 4. Motor neurons in SBMA exhibit hyperexcitability at the ultra-early stage.
(A) Upregulation of excitatory synapse–related genes in SBMA.
(B) Evaluation of motor neuron activity using calcium imaging.

Finally, we investigated the relationship between motor neuron hyperexcitability at a very early stage and subsequent motor neuron degeneration at later stages in SBMA mice. Since Rest4, which upregulates excitatory synaptic genes, was elevated in early postnatal SBMA mice, we designed an ASO targeting Rest4 (Rest4-ASO) and administered it into the cerebral ventricles at P1. Rest4-ASO reduced Rest4 expression, suppressed the expression of excitatory synaptic genes, and alleviated motor neuron

hyperexcitability in SBMA mice one week after administration (Fig. 5A). Long-term follow-up revealed that neonatal administration of Rest4-ASO improved both survival and motor function in SBMA mice (Fig. 5B).

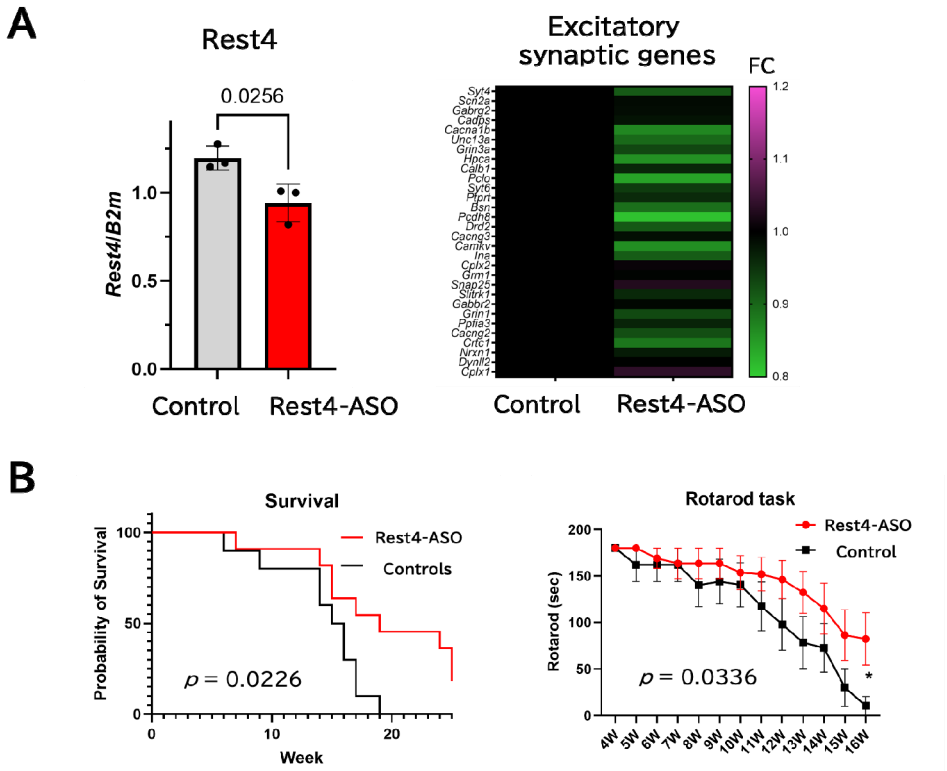

Fig. 5. Reducing excitatory synaptic genes at the ultra-early stage improves survival and motor function in SBMA mice.
(A) Reduction of excitatory synaptic genes by Rest4-ASO at postnatal day 1.
(B) Rest4-ASO extends survival and improves motor function in SBMA mice.

Research Summary and Future Perspective

In summary, this study revealed that motor neurons in neonatal SBMA mice and those derived from patients' iPSCs exhibit hyperexcitability due to increased expression of excitatory synaptic genes. ASO-mediated reduction of mutant AR or excitatory synaptic gene expression alleviated this hyperexcitability and ameliorated subsequent motor neuron degeneration (Fig. 6). Moving forward, we aim to evaluate the safety of nucleic acid–based therapeutics and the efficacy of repeated administration. We also intend to identify biomarkers that can serve as indicators for pre-symptomatic intervention, thereby contributing to the development of early therapeutic strategies for SBMA. Because neuronal hyperexcitability in the early stages of disease is a phenomenon common to many neurodegenerative disorders, this study may also contribute to elucidating the pathogenesis of other diseases and to the development of early therapeutic strategies.

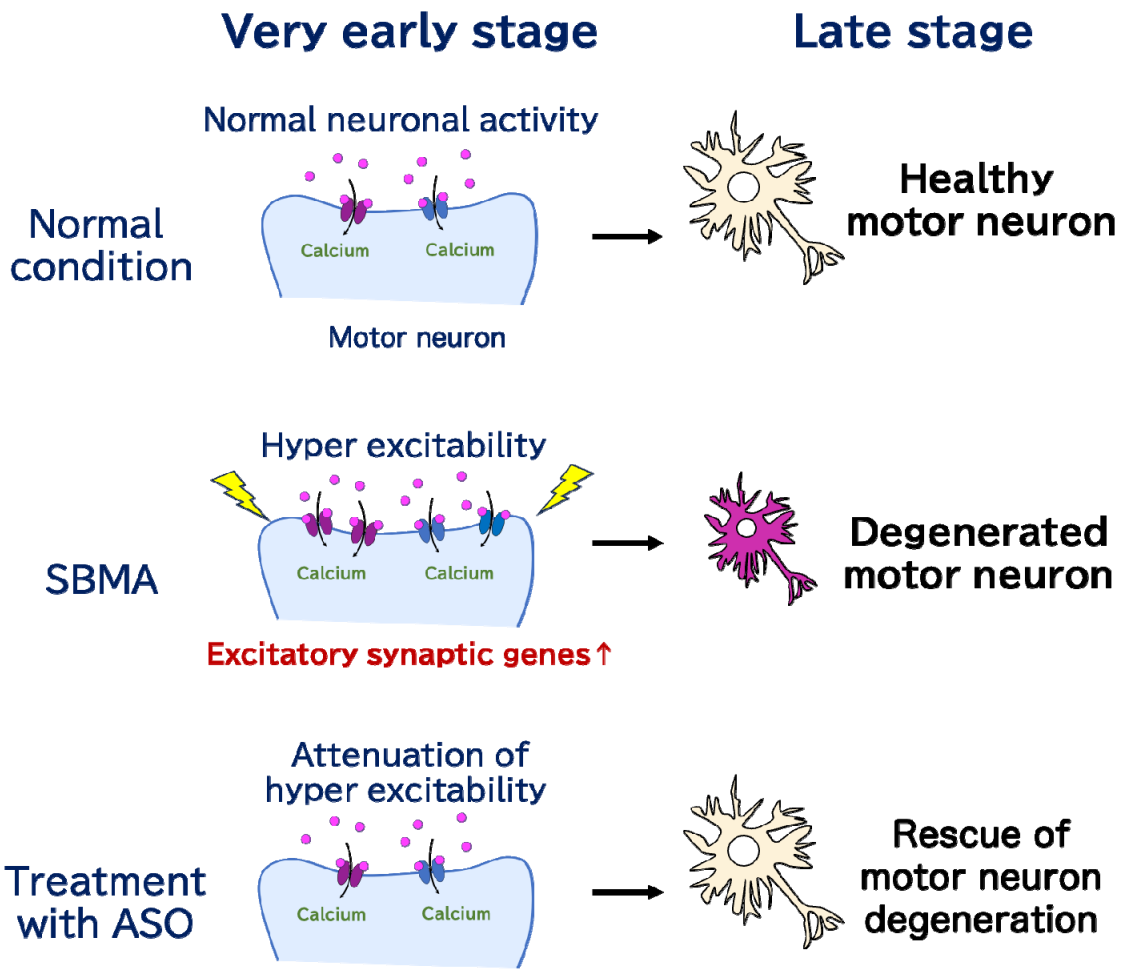

Fig. 6. Summary of this study

Publication

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