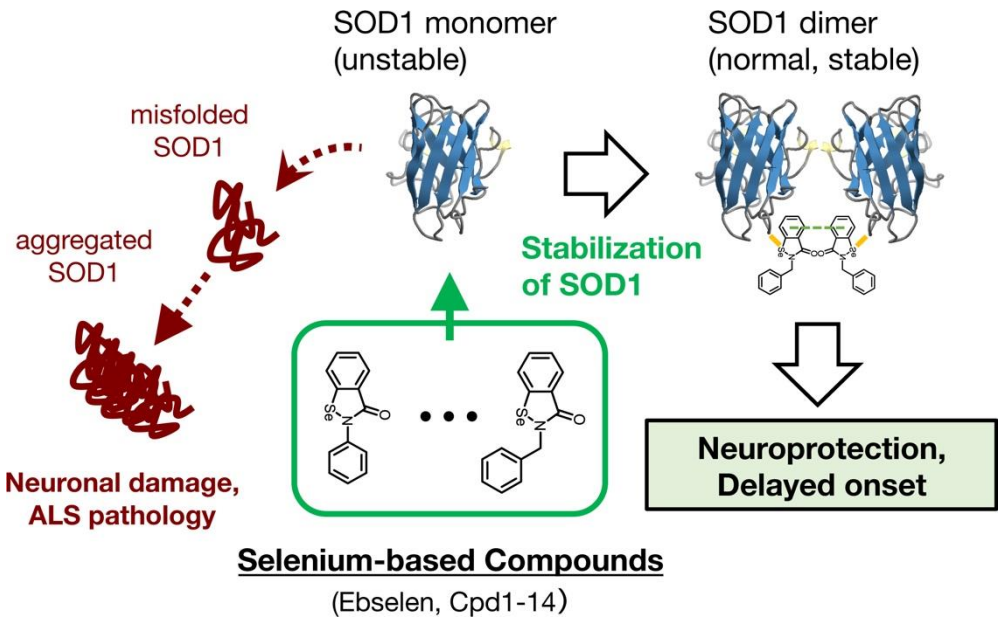

News Release

Title

Novel Selenium-based compounds with therapeutic potential for ALS

Key Points

- New neuroprotective compounds against abnormal SOD1-mediated toxicity were developed based on ebselen.
- New compounds are promising for future candidate drug for ALS

Summary

ALS is a neurodegenerative disease which affects motor neurons and the links between our brain and our muscles with limited choice of therapy. Around 20% of the familial ALS cases arise from dominant mutations in the *SOD1* gene. Aggregation of mutant SOD1 protein in familial cases and of wild-type SOD1 in at least some sporadic ALS cases is one of the known causes of the disease. Stabilisation of the original SOD structure is seen as a key strategy to avoid aggregation. The international team led by Professor Samar Hasnain in University of Liverpool and Professor Koji Yamanaka in Research Institute of Environmental Medicine, Nagoya University and Nagoya University Graduate School of Medicine has developed a number of ebselen-based compounds with improvements in SOD1 stabilisation and in vitro therapeutic effects with significantly better potency than edaravone. Structure-activity relationship of hits has been guided by high resolution structures of ligand-bound mutant form of SOD1 protein. They were also able to show clear effect of ebselen on delaying disease onset in ALS model mouse, holding encouraging promise for potential therapeutic compounds.

Main text of News release

Scientists have taken a significant step forward in the search to find effective new drug targets for motor neurone disease.

Researchers from Nagoya University (Japan) and the Universities of Liverpool (UK) have shown that a Selenium-based drug-molecule called ebselen and a number of other novel compounds developed at Liverpool can change many of the toxic characteristics of a protein, superoxide dismutase (SOD1), which causes some cases of Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease.

Research Background

ALS is a neurodegenerative disease which affects motor neurons and the neuronal links between our brain and our muscles. Over the course of the disease these nerve links die, and the patient becomes paralysed, with the majority dying within 2 to 5 years of diagnosis. Around 20% of the familial ALS cases arise from dominant mutations in the *SOD1* gene. Aggregation of mutant SOD1 protein in familial cases and of wild-type SOD1 in at least some sporadic ALS cases is one of the known causes of the disease. Riluzole, approved in 1995 and edaravone in 2017 remain the only drugs with limited therapeutic benefits.

Research Results

Stabilisation of the original SOD structure is seen as a key strategy to avoid aggregation. The team have developed a number of ebselen-based compounds with improvements in SOD1 stabilisation and *in vitro* therapeutic effects with significantly better potency than edaravone. Structure-activity relationship of hits has been guided by high resolution structures of ligand-bound A4V SOD1, a mutant which causes the most severe disease. They were also able to show clear effect of ebselen on delaying disease onset in an ALS model mouse, holding encouraging promise for potential therapeutic compounds.

Professor Samar Hasnain, who led the international team of interdisciplinary experts said: "The fact that this new generation of organo-selenium compounds have better *in vitro* neuroprotective activity than edaravone holds a significance promise for the potential of this class of compounds as an alternative therapeutic agent for ALS treatment.

"The ability of these compounds to target cysteine 111 in SOD may have wider therapeutic applications targeting cysteines of enzymes involved in pathogenic and viral diseases including the main protease of SARS-Cov-2 (COVID-19)."

Professor Paul O'Neill, who lead the medicinal chemistry programme said: "Our medicinal

chemistry approach, guided by protein-ligand crystallography studies, focused on the design of ebselen based analogues that have improved *in vitro* potency coupled with excellent predicted CNS exposure and improved solubility and metabolic stability characteristics. By employing this multi-parameter optimisation approach to drug design, the next key stage will be to screen our next generation compounds in appropriate disease models."

Professor Koji Yamanaka, a physician-neuroscientist at Nagoya University, said: "It is very encouraging that a number of these novel Selenium compounds exhibited better *in vitro* neuroprotection in mouse neuronal cells than edaravone. *In vivo* disease onset delay by ebselen has been demonstrated for the first time in ALS mouse model and further improvement can be expected from the new novel compounds in view of their improved in vitro protection. Choices are very limited for a current ALS therapy, therefore, we are excited to take a significant step forward for developing a new class of drug candidate for ALS."

Dr. Kangsa Amporndanai, lead author and a post-doctoral fellow supported by an ALSA grant, said "It is exciting for me to be a part of the UK-Japan collaborative research team developing novel druggable compounds for ALS. Hopefully, one of this class of compounds would be a promising candidate in clinical study that able to help ALS patients." Dr. Seiji Watanabe, an assistant professor in Yamanaka's group at Nagoya University, who is a co-first author of the study, said: "I'm so honoured to join this study. The tremendous international collaboration between the UK and Japan enabled us to reach an important milestone. I hope we can make a further achievement on the ALS therapy via the successive collaboration in the future."

The work was supported by a grant from the MEXT, Japan and the ALS Association, USA. The study, 'Novel Selenium-based compounds with therapeutic potential for SOD1-linked Amyotrophic Lateral Sclerosis' is published in the journal *EBioMedicine* on August 28.

Publication

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