Repurposing Segesterone Acetate (Nestorone®) as a Potential Neuroprotective Drug

By: Dr. Gurmeet Kaur Surindar Singh

Neurodegenerative diseases affect an estimated 30 million people worldwide, with the number expected to increase to 150 million by 2050. Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis are all neurodegenerative diseases characterized by the accumulation of misfolded protein aggregates in specific brain regions. The challenges in developing new drugs for neurodegenerative diseases, due to the costly and time-consuming nature of preclinical and clinical trials, exacerbate the escalating global health challenge. Consequently, drug repurposing, or the additional utilization of existing drugs, presents itself as a favourable option for addressing these challenges, especially given that their safety has already been established.

Segesterone acetate (16-methylene-17alpha-acetoxy-19-norpregn-4-ene-3,20-dione), which is better known as Nestorone® (NES), has been approved by the Food and Drug Administration (FDA) for use as a vaginal contraceptive in humans (Nelson, 2019). NES, a synthetic norpregnane derived from 19-norprogesterone, exhibits highly selective progesterone receptor agonism, bypassing most other receptors, including androgenic, estrogenic, or glucocorticoid-like effects. Notably, it is a promising candidate for long-term use, effective, and has reduced potential side effects (Kumar et al., 2017). Progesterone receptors are not only found in the cells of the female reproductive system but also in multiple organ systems, including the brain. Because of its high specificity for progesterone receptors and potent activity even at low doses, NES holds promise as a neuroprotective drug.

The potential for repurposing this contraceptive drug eliminates certain lengthy preclinical testing processes, possibly reducing the phases of clinical trials. This approach also circumvents the costly drug development process for pharmaceutical companies. Furthermore, various routes of administration have demonstrated the safety of NES. Given the potential use of progesterone as a treatment for neurological diseases (Atif et al., 2020; Wali et al., 2016), the utilization of NES in stroke and multiple sclerosis has gained interest. NES provides protection against pathogenic circumstances that lead to inflammation, motor neuron cell loss, and demyelination (Lee et al., 2022).

Other neurodegenerative disorders involving neurogenesis, like AD, may benefit from this progesterone receptor agonist. Neurodegenerative diseases encompass the accumulation of specific proteins and complex anatomical pathology. Despite their complexity, these diseases share the common outcome of progressively occurring neuronal dysfunction and eventual death. Thus, we proposed to explore the possible neuroprotective properties of NES in rodent models with AD and vascular dementia pathologies. The authors would like to convey their sincere gratitude to the Ministry of Higher Education (MoHE) for providing the funding for this study under the Fundamental Research Grant Scheme (FRGS) 2023-2026 (FRGS/1/2023/SKK10/UITM/02/2).

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