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Geroprotection in the future.

In memoriam of Joseph Knoll: the selegiline story continues

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Some centuries ago human life expectancy was about 30-40 years. The developments in hygiene and pharmacotherapy it started to increase in the 19th century in the industrialized countries and for today it is more than doubled. Prolonging the global average human life span will raise many social and health challenges. In the ageing population the prevalence of neurodegenerative diseases, tumor manifestations and organ damages is much higher, thus, in the 21th century the development of the anti-ageing therapy and geroprotection will be one of the most significant healthcare tasks to be solved (Global Burden of Disease Study (GBD) - 2015, 2016; Ho and Hendi, 2018).

Putative catecholaminergic enhancer regulation by selegiline?

More than 50 years ago, Knoll and his team developed selegiline/(-)-deprenyl as the first selective irreversible inhibitor of B-type monoamine oxidase (MAO-B) to treat depression and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases (Knoll et al., 1965; Knoll and Magyar, 1972). Since then, selegiline became a worldwide used drug in Parkinson's disease and major depression. Knoll hypothesized later that phenylethylamine (PEA), the physiologically important trace amine in the brain known as a releaser of catecholamines, is a unique catecholaminergic activity enhancer substance in low concentration, when it does not induce catecholamine release. This "enhancer" effect remained undetected because of its direct catecholamine-releasing effect concealed it. Selegiline/(-)-deprenyl, the first PEA-derivative devoid of the catecholamine releasing property allowed discovering the putative "enhancer regulation" in the brain (Knoll et al., 1996).

The development of (2*R*)-1-(1-benzofuran-2-yl)-*N*-propylpentan-2-amine (BPAP), a hundred times more potent selective synthetic enhancer substance than selegiline/(-)-deprenyl, is now the best experimental tool to detect the enhancer-sensitive regulations in the

mammalian brain (Knoll et al., 1999). Denes et al. demonstrated the enhancer-sensitivity of human brain endothelial cells (2006). Another study suggested the potential use of combined selegiline and stem cell therapy to improve neurotrophins deficits in neurodegenerative diseases in ageing (Esmaeili et al., 2006).

Role of the catecholaminergic enhancer regulation in ageing

The age-related decay in the brain's PEA and dopamine supply are well-known biochemical deterioration of ageing. The deterioration in behavioral performances with ageing and longevity depends significantly on the pace of the worsening of these biochemical changes. Selegiline/(-)-deprenyl increasing the supply of the brain with PEA and dopamine counteracts this ageing process. Maintenance of male rats from sexual maturity until death on selegiline/(-)-deprenyl slows the age-related decline of learning ability and prolongs life (Knoll and Miklya, 2016).

Knoll proposed 34 years ago to slow the ageing of the brain, the decay of behavioral performances, prolong life, and prevent or delay the onset of age-related neurodegenerative diseases such as Parkinson’s and Alzheimer’s via the prophylactic daily administration of 1 mg selegiline/(-)-deprenyl (Knoll 1985; Miklya 2011). Selegiline/(-)-deprenyl also belongs to the anti-ageing drugs but up to the present, a randomized controlled clinical trial showing the capacity of selegiline/(-)-deprenyl to prevent or delay the onset of neurodegenerative diseases is still missing. Considering the rapid increase of the population over the age of 65, Knoll’s work might be a great promise for the future (Knoll 2016).

Prolongation of lifespan and tumor suppressing effect?

Knoll et al. demonstrated that selegiline/(-)-deprenyl enhances the activity of the catecholaminergic neurons in the brain stem already in femto-picomolar concentration ranges and this previously unknown “enhancer effect” leaves MAO-B activity unchanged. The

synthetic enhancer substances increase the impulse propagation generated release of the transmitter in the brain, thus the enhancer effect at least in part might be a central nervous system effect (Knoll et al., 1999). The longevity studies performed with enhancer doses of selegiline/(-)-deprenyl and BPAP showed that the rats lived significantly longer than their placebo-treated peers. This experimental evidence may suggest that at least in part, the specific enhancer effect may be responsible for the prolongation of lifespan by selegiline/(-)-deprenyl and BPAP (Knoll and Miklya, 2016).

Interestingly, in the longevity study in rats, selegiline/(-)-deprenyl and BPAP treatments at sub-monoamine oxidase inhibitory concentrations resulted in a significantly lower incidence of spontaneous tumor manifestations in the animals. Therefore, Knoll hypothesized an existence of an "enhancer-sensitive tumor-manifestation-suppressing" regulation (Knoll et al., 2017).

Conclusions and future directions

At the age of 93, Joseph Knoll, one of the founding members of the Hungarian Society for Experimental and Clinical Pharmacology and the member of the Hungarian Academy of Sciences died in 2018. The scientific world lost one of the pioneers of the field of neuropsychopharmacology, but the selegiline story continues. Despite being an old drug, the scientific interest in selegiline continues, as shown by increasing number of scientific publications including reviews and clinical trials using selegiline in different pathologies in the last 5 years. As an example, we have recently shown that selegiline reduced adiposity induced by high-fat, high-sucrose diet in male rats (Nagy et al, 2018). To develop new enhancer substances and to test the potential geroprotective efficacy of known "enhancer" substances such as selegiline and BPAP in different indications including potential tumor

preventing effect is of great interest (Knoll et al., 2017; US patent App.15/533,067; US patent App.15/533,091).

This paper is also dedicated to the memory of Fumio Yoneda, the Japanese chemist, who synthetized BPAP. He deceased in 2019.

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