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Psychotria nemorosa alkaloids induce metallothionein and reduce proteotoxicity in Caenorhabditis elegans models of Alzheimer's and Parkinson's diseases

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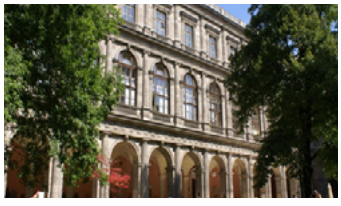
Abstract

In 2008, Bush and Tanzi proposed that a breakdown in metal homeostasis is the main cause of neurodegenerative diseases (NDs), and drugs restoring metal homeostasis are promising novel therapeutic strategies (1). The multipurpose protein metallothionein (MT), which participates in the transport, homeostasis, and detoxification of heavy metals was shown to be markedly diminished in brains of several NDs (2, 3). Recently we could show that MT in healthy C. elegans slightly increases with age whereas in amyloid ß (Aß) expressing worms an intense induction in the young adults was followed by a breakdown during ageing accompanied by an accumulation of iron, copper and manganese. Therefore, we hypothesized that prolonging the time span of MT release might be a promising therapeutic target in NDs (4). Here we investigated Psychotria nemorosa alkaloid fraction PN4FL-2b and three isolated alkaloids isolated from it for their ability to reduce proteotoxicity in C. elegans models of Alzheimer's disease (AD) and Parkinson's disease (PD) and to induce MT during ageing. Psychotria nemorosa alkaloids are known to inhibit butyrylcholinesterase (BChE), which is related to AD, as well as monoamine oxidase-A (MAO-A), which is related to PD (5). In the transgenic strain CL2659, expression of Aß in muscle cells led to a phenotypic paralysis after 48 hours. Compounds that encounter AD prolonged time until paralysis. For the PD assay we used C. elegans strain NL5901, where α-synuclein is GFP-tagged and can be monitored by a fluorescent reader. In the transgenic strain CL2120, MT is GFP tagged and Aß is expressed constitutively. So we could monitor MT induction until its breakdown which occurred after about 6 days. The alkaloid fraction PN4FL-2b and two main isolates, namely nemorosine A and fargesine, were able to significantly reduce Aß and α-synuclein proteotoxicity and prolonged time of MT induction in C. elegans. The results of this study reveal a significant MT induction for nemorosine A and fargesine, thus, adding a further mode of action to the main alkaloids of this medicinal plant.

Biography

Dagmar is a leading expert in C. elegans drug screening platforms and is responsible for the optimization and expansion of the Oxford Antibiotic Group's screening platforms. Dagmar has over ten years of experience in drug screens using antibacterial, antiviral and cellular assays. In her previous roles in biotech and pharma, Dagmar was involved in a number of drug development programs in antibiotics, and neurological disorders. Dagmar holds an MSc in neurobiology and a BSc. in biomedicine and biotechnology from the University of Vienna and works at the Department of Pharmacognosy at the University of Vienna while joining Oxford Antibiotics Group. For her PhD thesis, Dagmar was awarded a prestigious Doc-fellowship from the Austrian Academy of Sciences.



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