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INTRINSIC ACTIVITY

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MEETING ABSTRACT

A2.1

ENDF1, a hops-derived prenylated flavonoid, enhances neurite growth and complexity in DRG neurons despite extracellular matrix inhibitors

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Background: Restoration of neuronal connectivity after lesion of the central nervous system, such as spinal cord injury, is one of the biggest challenges in modern medicine. In particular, the accumulation of axon growth inhibitors at the site of injury constitutes a major obstacle to structural and thus functional repair. We identified a molecule called ENDF1, a prenylflavonoid from hops that is very potent in enhancing regrowth and branching of neurites from dorsal root ganglion neurons cultured over growth-promoting substrates. In the present study, we investigated ENDF1's capacity to promote regeneration of rat dorsal root ganglion neurons over the three main components of the extracellular matrix acting as axon growth inhibitors: semaphorin 3A, ephrin A4 and mixed chondroitin sulphate proteoglycans. In addition, we investigated for ENDF1's interaction with TrkA, the receptor of NGF, and for the phosphorylation of cofilin, a downstream effector of RhoA/Rock signalling, as two potential mediators of ENDF1's activity in neurons.

Methods: We seeded DRG neurons (rat P2) on each inhibitory substrate, *i.e.* semaphorin 3A, ephrin A4 and mixed chondroitin sulphate proteoglycans, and analysed the percentage of neurons displaying neurite regrowth. We measured the length of these neurites and counted the number of branching points, as a measure for complexity. For the analysis of signalling pathways, PC12 cells were treated with ENDF1 and analysed by western blotting.

Results: We report that ENDF1 application significantly increased the percentage of sensory neurons able to regrow their neurites despite the presence of ECM inhibitors, and this to an extent similar to the one obtained after NGF treatment (positive control). Moreover, ENDF1 strongly enhanced the total neurite length and the complexity of neurites extending from neurons challenged with axon growth inhibitors. Although the impacts of NGF and ENDF1 on the regeneration of DRG neurons were similar, the activity of ENDF1 was not mediated by signalling through the TrkA receptor, indicating that ENDF1 acts through a different signalling pathway than NGF. RhoA/Rock signalling is a cardinal pathway involved in axonal regeneration. However, treatment with ENDF1 did not decrease the phosphorylation of cofilin, as would result from a RhoA/Rock-dependent signalling.

Discussion: ENDF1 is a potent pro-neuroregenerative factor, acting on alternative pathways promoting neurite regrowth. Learning more about ENDF1's mode of action might open windows to identify novel targets for regenerative therapies of the nervous system.

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Keywords: flavonoids – dorsal root ganglia – axonal outgrowth – semaphorin 3A – ephrin A4 – chondroitin sulphate proteoglycans – CSPGs – neuroregeneration

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