Abstract

Neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, threaten the lives of millions of people and the number of affected patients is constantly growing with the increase of the aging population. Small molecule neurotrophic agents represent promising therapeutics for the pharmacological management of neurodegenerative diseases. In this study, a series of caffeic acid amide analogues with variable alkyl chain lengths, including ACAF3 (C3), ACAF4 (C4), ACAF6 (C6), ACAF8 (C8) and ACAF12 (C12) were synthesized and their neurotrophic activity was examined by different methods in PC12 neuronal cells. We found that all caffeic acid amide derivatives significantly increased survival in PC12 neuronal cells in serum-deprived conditions at 25 μM, as measured by the MTT assay. ACAF4, ACAF6 and ACAF8 at 5 μM also significantly enhanced the effect of nerve growth factor (NGF) in inducing neurite outgrowth, a sign of neuronal differentiation. The neurotrophic effects of amide derivatives did not seem to be mediated by direct activation of tropomyosin receptor kinase A (TrkA) receptor, since K252a, a potent TrkA antagonist, did not block the neuronal survival enhancement effect. Similarly, the active compounds did not activate TrkA as measured by immunoblotting with anti-phosphoTrkA antibody. We also examined the effect of amide derivatives on signaling pathways involved in survival and differentiation by immunoblotting. ACAF4 and ACAF12 induced ERK1/2 phosphorylation in PC12 cells at 5 and 25 μM, while ACAF12 was also able to significantly increase AKT phosphorylation at 5 and 25 μM. Molecular docking studies indicated that compared to the parental compound caffeic acid, ACAF12 exhibited higher binding energy with phosphoinositide 3-kinase (PI3K) as a putative molecular target. Based on Lipinski's rule of five, all of the compounds obeyed three molecular descriptors (HBD, HBA and MM) in drug-likeness test. Taken together, these findings show for the first time that caffeic amides possess strong neurotrophic effects exerted via modulation of ERK1/2 and AKT signaling pathways presumably by activation of PI3K and thus represent promising agents for the discovery of neurotrophic compounds for management of neurodegenerative diseases. © 2017 Elsevier Ltd