Natural Compound Berberine

Subjects: Pharmacology & Pharmacy
Contributor: PAOLA RUSMINI, Riccardo Cristofani

Accumulation of misfolded proteins is a common hallmark of several neurodegenerative disorders (NDs) which results from a failure or an impairment of the protein quality control (PQC) system. The PQC system is composed by chaperones and the degradative systems (proteasome and autophagy). Misfolded proteins are potentially neurotoxic, thus strategies aimed at preventing their aggregation or enhancing their clearance are emerging as interesting therapeutic targets for NDs. We tested the natural alkaloid berberine (BBR) and some derivatives (NAXs) for their capability to enhance misfolded proteins clearance in cell models of NDs. We found that both BBR and its semisynthetic derivatives promoted proteasomal degradation of mutant androgen receptor (ARpolyQ) causative of spinal and bulbar muscular atrophy, preventing its aggregation. Overlapping effects were observed on other misfolded proteins causative of amyotrophic lateral sclerosis, frontotemporal-lobar degeneration or Huntington disease, but with selective and specific action against each different mutant protein. BBR and NAX compounds induce the clearance of misfolded proteins responsible for NDs, representing potential therapeutic tools to counteract these fatal disorders.

Keywords: Misfolding ; neurodegeneration ; Spinal and bulbar muscular atrophy ; Protein aggregation ; Berberine ; Amyotrophic lateral sclerosis ; Frontotemporal dementia ; autophagy ; Proteasome

1. Introduction

This entry is related to the paper “Enhanced Clearance of Neurotoxic Misfolded Proteins by the Natural Compound Berberine and Its Derivatives” that has been published in *International Journal of Molecular Sciences* [1].

Accumulation of misfolded proteins is a common hallmark of several neurodegenerative disorders (NDs) which results from a failure or an impairment of the protein quality control (PQC) system, composed by the Ubiquitin Proteasome System (UPS) and the autophagic-lysosomal pathway (ALP). [2]. This may contribute to the pathogenesis of several neurodegenerative disorders (NDs), characterized by the progressive accumulation of damaged and misfolded proteins [3]. Among these diseases, the most common are Parkinson’s disease (PD), Alzheimer’s disease (AD), the class of polyglutamine (polyQ) diseases, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), etc. [4]. The polyglutamine-related diseases include Spinal and bulbar muscular atrophy (SBMA) and Huntington Disease (HD), characterized by an elongated polyQ tract in the Androgen receptor (AR) protein and in the Huntingtin protein (HTT), respectively. Despite the diverse aetiologies and the specific proteins involved, these NDs share a plethora of common characteristics and events that contribute to pathogenesis [5]. This may allow a possible common therapeutic approach aimed at stabilizing the native protein conformation, counteracting protein aggregation, or improving the misfolded protein clearance [6][7][8][9]

2. Aim

The aim of the present study was to test the natural alkaloid berberine (BBR) and some semisynthetic derivatives of BBR (NAXs) for their capability to enhance misfolded proteins clearance in cell models of NDs evaluating which degradative pathway mediates their action.

3. Results

We assayed BBR activity in a cellular model of SBMA targeting the mutant ARpolyQ that exerts neurotoxic activities in motoneurons causing the disease. Our data suggest that BBR enhances the degradation of mutant and misfolded ARpolyQ via the UPS, while ALP blockage does not counteract ARpolyQ clearance induced by BBR. These data are in line with a previous report showing that BBR is able to suppress wtAR signaling via UPS activity in prostate cancer [10].

The detailed mechanism of action of BBR on ARpolyQ is not clear totally yet, but a protein-specific activity of BBR on AR might be involved, since, in prostate cancer, BBR was shown to disrupt the interaction between AR and HSP90, the chaperone involved in folding and degradation of AR, and that plays a protective function in SBMA models [11][12][13][14][15].

In addition, we demonstrated that BBR induces the degradation of other misfolded proteins, such as the 25 kDa C-terminal fragment of TAR-DNA binding protein-43 (TDP-43), the TDP-25, involved in sporadic forms of ALS (sALS), as well as mutant Superoxide Dismutase 1 (SOD1) causative of some familial forms of ALS (fALS). Of note, we observed that the action of BBR seems to be rather specific, since we found that the levels of the endogenous SOD1 were not affected by BBR treatment, clearly indicating that BBR acts preferentially and specifically on misfolded protein clearance.

BBR was already proved capable to promote HTT clearance in models of HD by stimulating autophagy; however, we did not observed this effect possibly because of different BBR doses used [16].

Since we found positive effects of BBR in SBMA, we went further and analyzed three BBR semisynthetic derivatives NAXs compounds (NAX014, NAX035, NAX 117), which were designed to improve the activity of BBR in some tumors, such as colon, breast and pancreatic cancer. The NAXs are characterized by the presence of aromatic groups linked to the C-13 position, in order to allow additional non covalent interaction with the molecular targets [17][18][19].

Interestingly, we found that all NAXs reduced the number of cells bearing intracellular ARpolyQ aggregates, but only NAX014 induced a significant increase of the clearance of the mutant ARpolyQ. In addition, in cellular model of fALS expressing SOD1-G93A, all NAXs stimulated the degradation of mutant SOD1 and were found more potent than BBR. Conversely, in our cellular model of sALS (GFP-TDP25 expressing cells), only NAX014 exerted effects similar to BBR, while NAX035 was the unique compound effective in the clearance of mutant HTT in HD cell model. Therefore, these compounds seem to have a selective activity in response to specific misfolded proteins, for example NAX014 is effective on AR.Q46, TDP-25 and mutant SOD1, while it is ineffective or even detrimental on mutant HTT accumulation.

4. Conclusions

In this work, for the first time it has been demonstrated the beneficial effect of BBR and semisynthetic derivatives in the clearance of ARpolyQ in motoneuronal cells. While NAXs have been already tested in different types of cancer, this is the first report showing their potential use also in NDs. Some NAXs were found to have similar or more potent effects than BBR, but with different specific activities depending upon the misfolded protein target evaluated, suggesting that these compounds might be selective for mutant proteins. Given the pleiotropic and cell-specific effects exerted by BBR, and the different effects observed by NAXs treatment on misfolded protein clearance, future perspectives will be focused on unraveling the detailed mechanism of action of BBR on misfolded protein clearance, and, moreover, on understanding the different and specific activity of NAXs. It is possible that the different NAXs might activate different intracellular pathways leading to a selective clearance of misfolded proteins.

Compounds able to enhance misfolded protein clearance result in being very attractive for NDs. In this line, the use of compounds able to cross the blood brain barrier might represent a safe and useful treatment alone or in combination with other drugs.

References

1. Rusmini, P.; Cristofani, R.; Tedesco, B.; Ferrari, V.; Messi, E.; Piccolella, M.; Casarotto, E.; Chierichetti, M.; Cicardi, M. E.; Galbiati, M.; et al. Enhanced Clearance of Neurotoxic Misfolded Proteins by the Natural Compound Berberine and Its Derivatives. Int J Mol Sci 2020, 1–19. https://doi.org/doi: 10.3390/ijms21103443.
2. Chen, B.; Retzlaff, M.; Roos, T.; Frydman, J. Cellular Strategies of Protein Quality Control. Cold Spring Harb Perspect Biol 2011, 3 (8), a004374.
3. Ross, C. A.; Poirier, M. A. Protein Aggregation and Neurodegenerative Disease. Nat Med 2004, 10 Suppl, S10-7. https://doi.org/10.1038/nm1066nm1066
4. Cox, D.; Raeburn, C.; Sui, X.; Hatters, D. M. Protein Aggregation in Cell Biology: An Aggregomics Perspective of Health and Disease. Semin. Cell Dev. Biol. 2018. https://doi.org/10.1016/J.SEMCDB.2018.05.003.
5. Winklhofer, K. F.; Tatzelt, J.; Haass, C. The Two Faces of Protein Misfolding: Gain- and Loss-of-Function in Neurodegenerative Diseases. EMBO J. 2008, 27 (2), 336–349. https://doi.org/10.1038/sj.emboj.7601930.
6. Rusmini, P.; Cortese, K.; Crippa, V.; Cristofani, R.; Cicardi, M. E.; Ferrari, V.; Vezzoli, G.; Tedesco, B.; Meroni, M.; Messi, E.; et al. Trehalose Induces Autophagy via Lysosomal-Mediated TFEB Activation in Models of Motoneuron

Degeneration. Autophagy 2019, 15 (4), 631–651. https://doi.org/10.1080/15548627.2018.1535292.

7. Cristofani, R.; Crippa, V.; Rusmini, P.; Cicardi, M. E.; Meroni, M.; Licata, N. V.; Sala, G.; Giorgetti, E.; Grunseich, C.; Galbiati, M.; et al. Inhibition of Retrograde Transport Modulates Misfolded Protein Accumulation and Clearance in Motoneuron Diseases. Autophagy 2017, 13 (8). https://doi.org/10.1080/15548627.2017.1308985.
8. Tanaka, K.; Matsuda, N. Proteostasis and Neurodegeneration: The Roles of Proteasomal Degradation and Autophagy. Biochim. Biophys. Acta - Mol. Cell Res. 2014, 1843 (1), 197–204. https://doi.org/10.1016/J.BBAMCR.2013.03.012.
9. Giorgetti, E.; Rusmini, P.; Crippa, V.; Cristofani, R.; Boncoraglio, A.; Cicardi, M. E.; Galbiati, M.; Poletti, A. Synergic Prodegradative Activity of Bicalutamide and Trehalose on the Mutant Androgen Receptor Responsible for Spinal and Bulbar Muscular Atrophy. Hum. Mol. Genet. 2015, 24 (1). https://doi.org/10.1093/hmg/ddu419.
10. Li, J.; Cao, B.; Liu, X.; Fu, X.; Xiong, Z.; Chen, L.; Sartor, O.; Dong, Y.; Zhang, H. Berberine Suppresses Androgen Receptor Signaling in Prostate Cancer. Mol Cancer Ther 2011, 10 (8), 1346–1356. https://doi.org/10.1158/1535-7163.MCT-10-0985.
11. Waza, M.; Adachi, H.; Katsuno, M.; Minamiyama, M.; Tanaka, F.; Sobue, G. Alleviating Neurodegeneration by an Anticancer Agent: An Hsp90 Inhibitor (17-AAG). Ann N Y Acad Sci 2006, 1086, 21–34. https://doi.org/10.1196/annals.1377.012.
12. Rusmini, P.; Simonini, F.; Crippa, V.; Bolzoni, E.; Onesto, E.; Cagnin, M.; Sau, D.; Ferri, N.; Poletti, A. 17-AAG Increases Autophagic Removal of Mutant Androgen Receptor in Spinal and Bulbar Muscular Atrophy. Neurobiol Dis 2011, 41 (1), 83–95. https://doi.org/S0969-9961(10)00295-0 [pii]10.1016/j.nbd.2010.08.023.
13. Adachi, H.; Waza, M.; Tokui, K.; Katsuno, M.; Minamiyama, M.; Tanaka, F.; Doyu, M.; Sobue, G. CHIP Overexpression Reduces Mutant Androgen Receptor Protein and Ameliorates Phenotypes of the Spinal and Bulbar Muscular Atrophy Transgenic Mouse Model. J Neurosci 2007, 27 (19), 5115–5126. https://doi.org/10.1523/JNEUROSCI.1242-07.2007.
14. Pratt, W. B.; Gestwicki, J. E.; Osawa, Y.; Lieberman, A. P. Targeting Hsp90/Hsp70-Based Protein Quality Control for Treatment of Adult Onset Neurodegenerative Diseases. Annu. Rev. Pharmacol. Toxicol. 2015, 55, 353–371. https://doi.org/10.1146/annurev-pharmtox-010814-124332.
15. Thomas, M.; Harrell, J. M.; Morishima, Y.; Peng, H. M.; Pratt, W. B.; Lieberman, A. P. Pharmacologic and Genetic Inhibition of Hsp90-Dependent Trafficking Reduces Aggregation and Promotes Degradation of the Expanded Glutamine Androgen Receptor without Stress Protein Induction. Hum Mol Genet 2006, 15 (11), 1876–1883. https://doi.org/ddl110 [pii]10.1093/hmg/ddl110.
16. Jiang, W.; Wei, W.; Gaertig, M. A.; Li, S.; Li, X.-J. Therapeutic Effect of Berberine on Huntington's Disease Transgenic Mouse Model. PLoS One 2015, 10 (7), e0134142. https://doi.org/10.1371/journal.pone.0134142.
17. Pierpaoli, E.; Damiani, E.; Orlando, F.; Lucarini, G.; Bartozzi, B.; Lombardi, P.; Salvatore, C.; Geroni, C.; Donati, A.; Provinciali, M. Antiangiogenic and Antitumor Activities of Berberine Derivative NAX014 Compound in a Transgenic Murine Model of HER2/Neu-Positive Mammary Carcinoma. Carcinogenesis 2015, 36 (10), 1169–1179. https://doi.org/10.1093/carcin/bgv103.
18. Abrams, S. L.; Follo, M. Y.; Steelman, L. S.; Lertpiriyapong, K.; Cocco, L.; Ratti, S.; Martelli, A. M.; Candido, S.; Libra, M.; Murata, R. M.; et al. Abilities of Berberine and Chemically Modified Berberines to Inhibit Proliferation of Pancreatic Cancer Cells. Adv. Biol. Regul. 2019, 71 (October 2018), 172–182. https://doi.org/10.1016/j.jbior.2018.10.003.
19. Pierpaoli, E.; Fiorillo, G.; Lombardi, P.; Salvatore, C.; Geroni, C.; Piacenza, F.; Provinciali, M. Antitumor Activity of NAX060: A Novel Semisynthetic Berberine Derivative in Breast Cancer Cells. BioFactors 2018. https://doi.org/10.1002/biof.1440.
20. Guamán Ortiz, L. M.; Tillhon, M.; Parks, M.; Dutto, I.; Prosperi, E.; Savio, M.; Arcamone, A. G.; Buzzetti, F.; Lombardi, P.; Scovassi, A. I. Multiple Effects of Berberine Derivatives on Colon Cancer Cells. Biomed Res. Int. 2014, 2014, 924585. https://doi.org/10.1155/2014/924585.
