BMC Pharmacology

Meeting abstract

Modulation of multidrug resistance proteins by statins in human neuroblastoma

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from 14th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Innsbruck, Austria. 21–22 November 2008

Published: 5 November 2008

BMC Pharmacology 2008, **8**(Suppl 1):A24 doi:10.1186/1471-2210-8-S1-A24

This abstract is available from: http://www.biomedcentral.com/1471-2210/8/S1/A24

Chemoresistance is a major problem during cancer treatment. ATP-binding cassette (ABC) transporter efflux is mainly responsible for this chemotherapeutics resistance of the tumour cells. We have recently observed that in the presence of statins SH-SY5Y neuroblastoma cells show enhanced susceptibility to doxorubicin-induced apoptosis which cannot be explained by simple additivity. In order to monitor ABC transporter activity as a possible source of statin-mediated additivity in doxorubicin-induced apoptosis, calcein uptake and release were analysed in human SH-SY5Y neuroblastoma cells. Simvastatin inhibited calcein uptake and release to the same extent as the well-described 1st generation ABC transporter inhibitor verapamil. Using the fluorescence behaviour of doxorubicin the accumulation of the anthracycline in SH-SY5Y neuroblastoma cells was visualised by confocal microscopy. The cumulating fluorescence intensity showed significant acceleration and accumulation under atorvastatin treatment. P-glycoprotein (ABCB1) is a heavyly glycosylated transporter for cytotoxic compounds. The protein appears as a double band, representing a mature fully glycosylated protein (~180 kDa) and a partially deglycosylated immature protein (~140 kDa) [1]. Atorvastatin reduced the mature 180 kDa protein band, suggesting an impairment of glycosylation. Treatment of the cells with tunicamycin, an inhibitor of the endogenous protein glycosylation in the endopolasmic reticulum, leads to the detection of the complete deglycosylated immature protein (~110 kDa). This assumption is corroborated by additional N-glycosidase F (PNGase) treatment of the human SH-SY5Y cells. The functional relevance of the deglycosylation of P-glycoprotein has been confirmed by enhanced doxorubicin accumulation in PNGase F-treated SH-SY5Y cells. In order to circumvent limited biological significance of the degenerated SH-SY5Y cell line primary human neuroblastoma cells were investigated. Similary, in the presence of statins enhanced doxorubicin accumulation was detectable and thereby corroborated the above described principle of action. Taken together, simvastatin and atorvastatin reduce the glycosylation of P-glycoprotein. Hence, statins reduce the activity of P-glycoprotein, which leads to an enhanced intracellular accumulation of doxorubicin. This explains the potentiated apoptosis by co-application of simvastatin and doxorubicin.

Acknowledgements

The work was supported by the Herzfeldersche Familienstiftung and the GENAU-Dragon Project.

References

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