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Methylxanthines as modulators of anthracycline antibiotics and aromatic mutagens – analysis of interactions with DNA and biological activity

Abstract

Xenobiotics are exogenic chemical compounds present in the human body. One of the most prominent groups of xenobiotics are aromatic ligands that include anthracycline antibiotics. One of mechanisms of aromatic ligands action on the cellular level are direct interactions with DNA (intercalation, but also e.g. binding to the minor or major DNA groove) – therefore the same mechanism contributes to carcinogenesis and is used in cancer treatment. Simultaneously, a large group of biologically active aromatic compounds (e.g. methylxanthines) may influence direct interactions of aromatic ligands with DNA. Mechanism of this phenomenon is still subject of the intense debate, however, most probably, it bases on formation of mixed aggregates between aromatic ligands and modulating compounds, which leads to temporary reduction of the concentration of free, active form of ligand. It leads to the hypothesis that administration of aromatic anticancer antibiotics together with pentoxifylline may reduce side effects of the therapy (e.g. tissue necrosis at the site of injection) without reducing its anticancer activity.

To analyze the influence of methylxanthines (caffeine, pentoxifylline, thoephylline) on the direct interactions between selected aromatic ligands (model mutagen ICR-191, model fluorophore ethidium bromide, and anthracycline antibiotics doxorubicin and idarubicin) and DNA as well as biological effects of such interactions I employed a wide variety of biophysical and biological methods, starting from spectrophotometric measurements, via computational methodology (statistical-thermodynamical models) and isothermal titration calorimetry, mutagenicity tests on the prokaryotic organisms (Ames test) to analyzes on the eukaryotic cells (cytotoxicity assays, flow cytometry, confocal microscopy). Quantitative analysis of interactions in the mixture containing anthracycline antibiotics, DNA, and pentoxifylline required us to develop novel statistical-thermodynamical model allowing specification of concentration of four ligand forms in the mixture – namely, free (monomeric) form, dimeric form, ligand complexed with DNA and ligand complexed with pentoxifylline.

I calculated the interaction parameters of chosen aromatic ligands with methylxanthines and DNA. In the biological assays I observed protective effects of methylxanthines towards ICR-191 mutagenicity in the procaryotic mutagenicty test as well as pentoxifylline towards anthracycline antibiotics in both in the procaryotic mutagenicty test as well as cytotoxicity test on the human keratinocytes. Interestingly, I did not observe similar reduction of doxorubicin cytotoxic activity in the presence of pentoxifylline towards two selected cancer cell lines. Obtained results confirm stated hypothesis, however, obtained results has to be confirmed in the following research on the animal models.