INVESTIGATION OF COLISTIN EFFECTS ON MOUCE WHOLE BRAIN METABOLOME USING ^{1}H 1D NMR PROFILING

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The significant rise of bacterial pathogens with high resistance to common antibiotics constitutes a growing public health issue. Since few novel antibiotic classes reach the drug [discovery] pipeline, old antibiotics can provide an alternative. Polymyxin E, also known as colistin, has been used effectively for the treatment of infections caused by multidrug-resistant bacteria as a last-resort drug, with its clinical use recommending caution due to the induced nephrotoxicity and neurotoxicity. Metabolomics is a recent branch of omic technologies, that provides rapid, systematic and comprehensive profiling of all low molecular weight molecules in a multitude of biological samples, thus being able of deciphering the molecular mechanisms underlying to toxicity phenomena.
In the present study, metabolomics of whole brain tissue was employed to assess the effect of parental administration of the clinically used inactive prodrug known as colistin methanesulfonate (CMS), into two doses, one therapeutic and one toxic, in C57Bl/6 mice. The experimental animals were divided into three groups: control group (CTR, n=5) receiving only normal saline, therapeutic dose group receiving 1 mg/kg of the drug (CTH, n=5) and the toxicity group receiving a toxic dose of 1.5 mg/kg (CTOX, n=5). At the end of the administration the animals were sacrificed, the brain was excised as whole, homogenized and the polar metabolites were extracted applying a three-solvent protocol (a modification of the Bligh Dier protocol). Spectra were transformed to numerical data and subjected to uni- and multiparametric analyses for the detailed description of metabolites alteration related to colistin treatment.
^{1}H NMR metabolomic profiling of brain provides a very sensitive and powerful tool because a wide range of metabolites are brain-specific including neuron markers, neurotransmitters, as well as essential components of cellular membranes. 42 metabolites were unambiguously identified including amino acids and neurotransmitters, nucleotides and nucleocides, organics acids and cholines. All metabolites showed high variability in the three investigated groups, which, in combination with the small number of samples, rendered the statistical analysis a quite difficult task. Both analyses highlighted the important role of acetic acid and phosphocholine. Acetic acid showed a significant decrease in CTOX group, and this may reflect a switch of brain energy metabolism caused by destabilization of mitochondrial activity. Concerning phosphocholine, a statistically significant increase was observed in CTOX. Elevated phosphocholine in the brain is indicative of neurodegeneration, as a result of the disruption of the normal functioning of cell membranes. Further studies incorporating co-administration of compounds that increase the permeability of the Blood Brain Barrier to colistin could provide more valuable information regarding colistin neurotoxicity studies.