Studies into the mechanism of arsenic-induced neurotoxicity

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The aim of this study is to investigate the mechanism by which arsenic (As) induces its neurotoxic effects.

Background

The term 'neurotoxic' is used to describe a substance, condition or state that damages the nervous system and/or brain, usually by killing neurons. The term is generally used to describe a condition or substance that has been shown to result in observable physical damage.
Arsenic is a semi-metalloid and exposure to As is a world wide health problem causing various disorders and diseases in millions of people around the world. Arsenic causes various diseases such as numerous organ cancers and also patients show severe effects on their nervous system. The effects on the nervous system may be assessed with the use of clinical studies like nerve conduction velocities (NCV). In As exposed patients, their NCVs are diminished in comparison to healthy unexposed subjects. However, the mechanisms of As neurotoxicity remain somewhat obscure while the instance of As exposure, especially at chronic levels, remains a prevalent human health concern.
To start our investigation we had to ask the pertinent questions that comes with any investigations; why? How? And what kind of strategies must be taken?

Objectives and investigation of this thesis

As the molecular mechanism of arsenic neurotoxicity has not been described before, it was our aim to elucidate this mechanism. To start this investigation, we had to see whether the As effect that can be measured by reduced NCV, can be shown on molecular level in nerves. We devised studies in rats (*in vivo*) to determine the possible effects of As on the nervous system (Chapter 3 & 4). These studies were designed to answer whether As effects could be found on the nervous system and whether these effects could be established by different rout of exposure, dose and duration.
We studied the acute short effects of high As doses intravenously after a single exposure (Chapter 3) and the subchronic effects of intragastric administration of As for a longer exposure (Chapter 4). These studies deal with the effects of inorganic As in Wistar rats on the cytoskeletal protein composition of the sciatic nerve after acute and subchronic intoxication. The strategy in these two studies were to chart the pharmacokinetics in blood and urine and concentration in sciatic nerve and correlated them with effects that could arise on PNS with help of western blot technique on various cytoskeletal proteins.

After establishing the As effect *in vivo*, we started further investigation on the possible mechanisms of As neurotoxicity *in vitro*. *In vitro* studies were designed to study various As metabolites and compare their effects on genetic level for various cell cultures derived from neuroblastoma (SK-N-SH) or Schwannoma (ST-8814) representatives for nervous system, as well as non-neuronal derived cells such as, HeLA and Chinese Hamster Ovaries (CHO). These cell lines were chosen as a model for neurons as they harbor the mentioned neuro-cytoskeletal proteins like NFs and MAP-tau. We examined the (neuro-) toxic effects of various arsenic metabolites on these cells. The DNA expression levels of cytoskeletal proteins and genes involved in phosphorylation were studied after exposure to various arsenic metabolites and concentrations. The effects were examined on the relative quantification levels of the cytoskeletal genes, using Real-Time PCR (Chapter 5 & 6). To conclude these studies, the mechanism of NFs and MAP-tau phosphorylation was studied with the use of a p35 construct in HeLa cell line (Chapter 6). CHO cell lines such as AA8, UV20 and UV5 were also used to get additional information, especially to investigate effects of various As metabolites on the DNA repair mechanism namely nucleotide excision repair genes such as Ercc1 and Ercc2 (Chapter 7).