MEDICAL, HEALTH & PHARMACEUTICAL SCIENCES:

Arsenic Induced Autophagy in Developing Mouse Cerebellum: Involvement of Blood-Brain Barrier's Tight Junction Proteins and/or PI3K/Akt/mTOR Signaling Pathway

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Abstract: This study was designed to determine whether Blood-Brain Barrier's (BBB) Tight Junction Proteins (TJs) and/or PI3K/Akt/mTOR Signaling Pathway are involved during arsenic (As) induced autophagy in developing mice cerebellum after being exposed to different As concentrations [0, 0.15mg, 1.5mg and 15mg As(III)/L] during gestational and lactational periods. The dosage was continued to the pups till postnatal day (PND) 42.

Studies conducted at different developmental age points like PND21, PND28, PND35 and PND42 showed that exposure to As lead to a significant decrease in the mRNA expression levels of TJs (Occludin, Claudin, ZO-1 and ZO-2), PI3K, Akt, mTOR, and p62 with a concomitant increase in Beclin1, LC3I, LC3II, Atg5 and Atg12. Also, As significantly downregulated the occludin and mTOR protein expression levels with a concomitant upregulation of Beclin 1, LC3 and Atg12 in all the developmental age points. However, no significant alterations were observed in low and medium dose exposed groups of PND42. Histopathological analysis revealed the irregular arrangement of purkinje cell layer in the As exposed mice. Ultra structural analysis by transmission electron microscopy (TEM) revealed the occurrence of autophagosomes and vacuolated axons in the cerebellum of the mice exposed to high dose As at PND21 and 42 respectively.

Finally, we conclude that developmental As exposure significantly altered TJ proteins resulting an increase in BBB permeability, facilitating As to cross and induces autophagy which might be partly by inhibition of PI3K/Akt/mTOR signaling pathway in an age-dependent manner, i.e., PND21 mice were found to be more vulnerable to As-induced neurotoxicity which could be due to the immature BBB that allows As to cross through it. However, the effect was not significant in PND42, which could be due to the developed BBB.

***Keywords**: Arsenic, Autophagy, Blood-brain barrier, Cerebellum, Postnatal day*

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