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LETTER TO THE EDITOR

Metabolism of polyamines and oxidative stress in the brain of cholestatic rats

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Abstract In a recently published article in "Amino Acids" it was shown that obstructive jaundice of 9 days' duration in rats induces significant alterations of polyamines' metabolism in the brain, which might play an important pathogenetic role in cholestatic brain injury. The authors proposed that alterations of polyamines in cholestatic brain might induce neuronal toxicity through a mechanism that implicates the production of reactive oxygen species and oxidative stress, although this parameter was not evaluated in their study. This hypothesis is supported by our recent findings on brain oxidative status in rats with obstructive jaundice of 10 days' duration. Potential interrelations of the two studies' findings are discussed in this commentary.

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Dear Editor,

We read with great interest the recently published article in your journal, which evaluated the effect of extrahepatic cholestasis on metabolism of polyamines in the brain (Sokolovic et al. 2009). The authors, using an experimental model of obstructive jaundice induced by ligation of the common bile duct in Wistar rats, demonstrated that biliary obstruction of 9 days' duration induces significant alterations of polyamines' metabolism in the brain, which may play an important pathogenetic role in cholestatic brain injury. Specifically, it was found that spermidine, spermine and citrulline concentrations were decreased, whilst putrescine was increased. The activity of polyamine oxidase and arginase was increased and diamine oxidase was decreased. These alterations were prevented by administration of L-arginine, which might indicate its neuroprotective role in the brain during cholestasis.

Polyamines are possible neuroprotectors in the brain through anti-apoptotic and anti-oxidant mechanisms (Ha et al. 1998). Changes in their metabolism are connected to the degree of CNS impairment, because these molecules have an important role in degeneration of neurons (Henley et al. 1997). Alterations of polyamines seem to be a critical reaction of neurons to diverse types of injury, but whether this process is neurotoxic or neuroprotective is currently an issue of debate. The authors, discussing the results of their experiment, propose that alterations of polyamines in cholestatic brain might induce neuronal toxicity through a mechanism that implicates the production of reactive oxygen species and oxidative stress with subsequent activation of the apoptotic machinery. This view could be based on the fact that spermine, which is a potent antioxidant and free radical scavenger (Ha et al. 1998), was significantly decreased, whilst the activity of polyamine oxidase, which has the ability to

generate reactive oxygen species (Ivanova et al. 1998), was increased.

Estimation of brain oxidative stress was out of the purpose of the commented study, but our recently reported findings on brain oxidative status in cholestatic conditions might fill in the missing pieces of the puzzle (Chroni et al. 2006; Karageorgos et al. 2006). Specifically, in our experiments, using the same experimental model of bile duct-ligated Wistar rats and assessing brain oxidative status on the 10th day of biliary obstruction, we have shown the presence of increased oxidative stress in all brain areas examined (cerebral cortex, midbrain and cerebellum). Oxidative stress was evidenced by a significant decrease of the antioxidants reduced glutathione and protein thiols with parallel increase of the high oxidative stress markers lipid peroxidation and protein disulphides, whilst non-protein mixed disulphides were additionally increased in the midbrain in particular. Further evaluating the role of oxidative stress in jaundice-induced encephalopathy, in a subsequent study we provided direct evidence of brain oxidative stress in 10 days' cholestatic rats, demonstrating increased brain superoxide radical production (Konstantinou et al. 2008).

Therefore, alterations of brain polyamines metabolism and oxidative stress in extrahepatic cholestasis have been well demonstrated. These phenomena could be linked in two different ways: (1) primary alterations of polyamines induced by cholestasis might reduce the antioxidant capacity of brain tissue and promote oxidative stress and brain injury (Ha et al. 1998), or (2) cholestasis-induced brain oxidative stress and reactive oxygen species formation might act as intracellular messengers that regulate the expression of enzymes implicated in polyamines metabolism (Kuo et al. 1995), thus changing polyamines levels and promoting neurotoxicity. Further studies investigating in parallel oxidative stress and polyamines alterations in obstructive jaundice, with the potential use of modulators of both factors (antioxidants or polyamines substrates) could shed more light on our knowledge in the field.

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