

Reply to Dr Michaud *et al.*

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We thank Dr Michaud and colleagues [1] for their interest in our work and for their comments on the role of endoplasmic reticulum (ER) stress in the pathophysiology of amyotrophic lateral sclerosis (ALS). Their comments give us the opportunity to expand and clarify the potential neuroprotective effects of tauroursodeoxycholic acid (TUDCA).

It has been known for a long time that TUDCA has a possible cytoprotective and anti-apoptotic action on a variety of chronic neurodegenerative conditions [2]. The proposed mechanisms by which TUDCA protects from cell death include (i) inhibition of the mitochondrial apoptotic pathway through the inhibition of reactive oxygen species (ROS) production

and Bax translocation [3], (ii) inhibition of caspase-3 [4] and (iii) inhibition of ER stress via reduction of calcium efflux and caspase-12 activity [5]. With reference to the latter mechanism, it is notable that caspase-12 gene has a truncation mutation in the vast majority of the human population, leading to the production of a non-functional protein and suggesting that in humans other caspases mediate the ER stress induced apoptosis.

Mitochondria and ER are functionally and structurally related organelles [6]. For instance, mitochondrial-associated membranes are specialized contact points between mitochondria and ER, mediating important physiological and metabolic processes involving both organelles, such as calcium signaling, ROS production and apoptosis [7]. Notably, TUDCA has been shown to affect several of the processes involving both organelles.

In addition, several studies suggest that TUDCA can indeed prevent neuronal cell death by directly acting on mitochondrial targets, including data obtained in cellular and *in vivo* models of neurodegeneration [2]. Finally, TUDCA interferes with upstream targets of the mitochondria, including the E2F-1/p53/Bax pathway [8], and the role of p53 in mediating the effects of TUDCA has also been further confirmed using *in vitro* models of familial Alzheimer's disease [9].

Given the above considerations, we agree with Michaud *et al.* that TUDCA may have a role in reducing ER stress, but in our view this is just one of the possible targets in the complex biological context leading to cell death. We also agree that the cellular basis for the observed clinical effect warrants more investigations, including the measurement of ER stress levels and mitochondrial ROS production in peripheral blood mononuclear cells of patients, and that these parameters should be considered as secondary outcomes in future clinical trials on potential neuroprotective agents. The possibility exists that this clinical observation on the effects of TUDCA in

ALS may pave the way to a broader concept for the treatment of neurodegenerative disorders by acting on ER stress, mitochondrial ROS production or both.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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