Ursodeoxycholic acid as a potential alternative therapeutic approach for neurodegenerative disorders: Effects on cell apoptosis, oxidative stress and inflammation in the brain

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Abstract

Ursodeoxycholic acid (UDCA) is a bile acid component with anti-apoptotic, anti-oxidant and anti-inflammatory properties. It has been used in clinical medicine for liver diseases for centuries. In neurodegenerative diseases, increased cell apoptosis, oxidative stress and inflammation are frequently observed as well. Due to those beneficial effects of UDCA, recent studies have started to investigate the effects of UDCA in pre-clinical models of neurodegeneration. On this account, I review the data reported so far to investigate the role of UDCA in regulating apoptosis, oxidative stress and inflammation in pre-clinical models of neurodegeneration, as well as in homeostatic state. Evidence have shown that UDCA can reduce apoptosis, inhibit reactive oxygen species and tumor necrosis factor - \( \alpha \) production in neurodegenerative models. In addition, UDCA is able to induce apoptosis of brain blastoma cells in homeostatic conditions. Overall, this review suggests the therapeutic potential of UDCA in neurodegenerative disorders, proposing UDCA as a potential alternative therapeutic approach for patients suffering from these diseases.

Keywords

Ursodeoxycholic acid; Apoptosis; Oxidative stress; Inflammation; Neurodegeneration

1 Introduction

Ursodeoxycholic acid (UDCA) is an endogenous bile acid produced in small quantities in human bile and in larger quantities in certain species of bear bile (Qiao et al., 2011; Shoda, 1927; Tint et al., 1990). Dried bear bile (usually called bear bile powder) has been used...
medically to treat a variety of liver diseases in China for centuries (Beuers et al., 1998). Along with the rising concerns about endangered species, scientists have found alternative methods to artificially synthesize the active compound UDCA by chemically converting cholic acid and chenodeoxycholic acid from bovine bile (Eggert et al., 2014). Nowadays, UDCA is widely used in the treatment and management of cholestatic liver disease (Amaral et al., 2009), and it is the only first-line therapy approved by the US Food and Drug Administration (FDA) for primary biliary cholangitis. Meanwhile, its use has recently been extended to other liver diseases, such as intrahepatic cholestasis (Zhang et al., 2016), and even to extrahepatic diseases, such as inflammatory bowel disease (Van den Bossche et al., 2017) and sensory neuropathy (Park et al., 2008). This versatility is attributed to its multiple mechanisms of action, including reducing cell death, as well as exerting anti-oxidant and anti-inflammatory properties (Roma et al., 2011).

Whether being able to cross the blood-brain barrier is important for therapeutic molecules that act in the brain. Evidence suggests that UDCA can penetrate in the brain through the brain microvascular endothelium (Palmela et al., 2015). Apart from that, UDCA is able to enter the human cerebrospinal fluid after being given orally (Parry et al., 2010). Previous studies have suggested that innate UDCA can be detected in the brain and blood of mammals (Pan et al., 2017; Tao et al., 2021). Although the origin of brain UDCA is not yet clear, it is more likely that those innate UDCA enters the brain from the peripheral circulation (Kiriyama and Nochi, 2019). On the other hand, the possibility that UDCA synthesis also occurs in the brain should not be excluded.

Once in the brain, UDCA may play a role in neuroprotection, including reducing cell apoptosis (Amaral et al., 2009). For example, it was found that UDCA reduces neuronal loss in prion-infected cerebellar slice cultures (Cortez et al., 2015). In models of acute bilirubin encephalopathy, treatment with UDCA prevents the apoptosis induced by unconjugated bilirubin in astrocytes and foetal neurons isolated from rats (Silva et al., 2001).

Interestingly, increased cell apoptosis, oxidative stress and inflammation have been considered as three of the main pathophysiological mechanisms characterizing a wide range of brain diseases (Borsini et al., 2020; Cai and Xiao, 2016; Gelders et al., 2018; Hickey and Chesselet, 2003; Hilton et al., 2006; Jahanbazi Jahan-Abad et al., 2018; Jenner, 2003; Kohler et al., 2016; Liu et al., 2015, 2019; Rawat et al., 2018; Sanchez-Lopez et al., 2012; Xu et al., 2018). For instance, previous studies have found changed caspases in numerous brain diseases, which include major depressive disorder (Miguel-Hidalgo et al., 2014), Alzheimer’s disease (AD), brain trauma, Parkinson’s disease (PD) and so on (Friedlander, 2003). Similar to apoptosis, increased levels of oxidative stress products, as well as excessive production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IFN-γ are often observed in the neurological disorder of acute encephalitis/encephalopathy (Ichiyama et al., 1998), and in neurodegenerative disorders, like AD (Terranova et al., 2001) and PD (Chen et al., 2008), and in neuropsychiatric disorders, such as depression (Maes et al., 1998; Pariante, 2019; Pitharouli et al., 2021).

Considering UDCA have the ability to reduce apoptosis, oxidative stress and inflammation, recent studies have started to investigate the effects of UDCA on the above mechanisms.
in various brain diseases, especially in neurodegenerative disorders (Amaral et al., 2009; McMillin and DeMorrow, 2016). Therefore, with the intent of highlighting the role of UDCA as potential players in neurodegenerative disorders, I review the evidence reported so far to demonstrate the effect of UDCA on regulating cell apoptosis, oxidative stress, and inflammation in the brain, across in vivo, ex vivo and in vitro models of neurovegetative disorders, and in homeostatic state.

2 Effect of UDCA in models of neurodegenerative disorder

The potential protective role of UDCA in models of neurodegeneration has been extended to rotenone-induced models, 3-nitropropionic acid (3-NP)-induced models, amyloid-β (Aβ)-induced models, sodium nitroprusside (SNP)-induced models, 1-methyl-4-phenylpyridinium (MPP⁺)-induced models, and lipopolysaccharides (LPS)-induced models. Altogether, findings show that treatment with UDCA prevents increased apoptosis, oxidative stress, and inflammation caused by various challenges exposure to specific models of PD, AD, and Huntington’s disease (HD).

Three studies used treatment with Amyloid-β (Aβ) as a model of AD. One ex vivo study conducted in rats showed the capability of UDCA to inhibit apoptosis induced by Aβ in cortical neurons using Hoechst staining (Sola et al., 2006). Another ex vivo study found that UDCA prevents the production of interferon (IFN)-1β and nitric oxide (NO) in rat microglia previously exposed to Aβ (Joo et al., 2003). In addition, this study also showed that UDCA inhibits the production of the pro-inflammatory cytokine IL-1β and NO in LPS-exposed rat microglia (Joo et al., 2003), a model of neuroinflammation associated with neurodegeneration. Similarly, in an in vitro study that BV2 microglia previously exposed to Aβ, UDCA reduces the production of pro-inflammatory cytokines TNF-α and NO via inhibiting nuclear factor-κB (NF-κB) activation (Joo et al., 2004).

Three studies used three different toxicants (SNP, rotenone and MPP⁺, respectively) to model PD. In an in vitro study which used treatment with SNP as a model of PD (Chun and Low, 2012), UDCA significantly attenuates SNP-induced apoptosis in human neuroblastoma SH-SY5Y cells, such as nuclear fragmentation, caspase-3/7 and caspase-9 activation, and B-cell lymphoma 2 (Bcl-2)/Bcl-2 associated x (Bax) ratio decrease. In addition, treatment with SNP also induces oxidative stress in human neuroblastoma cell line SH-SY5Y, UDCA effectively attenuates the production of total reactive oxygen species (ROS), peroxynitrite and NO, and markedly inhibits the mitochondrial membrane potential loss and intracellular reduced glutathione depletion. In another in vivo study used treatment with rotenone as a model of PD in rats (Abdelkader et al., 2016), UDCA prominently improves mitochondrial function as verified by elevation of adenosine triphosphate (ATP) associated with preservation of mitochondrial integrity. Meanwhile, UDCA prevents alterations in Bax and Bcl-2 mRNA and reduces activation of caspase-9, caspase-8 and caspase-3. With respect to inflammation, UDCA reduces the rotenone-induced NF-κB mRNA expression and TNF-α, IL-1β, and IL-10 levels. In the third in vitro study used MPP⁺-treated mouse neuroblastoma (neuro-2a) cells to examine the effects of UDCA on PD pathogenesis, and findings showed that UDCA improves cell viability and decreases cell death in MPP⁺-
treated cells, inhibits ROS accumulation and ATP depletion in mouse neuroblastoma cells (Qi et al., 2021).

Lastly, one *in vitro* study which used treatment with 3-NP as a model of HD, results showed that UDCA prevents mitochondrial release of cytochrome c, a well-known indicator of oxidative stress, in rat neuronal RN33B cells (Rodrigues et al., 2000).

### 3 Effect of UDCA in homeostatic state

Although UDCA is a dihydroxy bile acid, it does not bind to the adsorbent, and its retention time is short, is hydrophilic, and devoid of cytotoxic properties in most model systems (Heikkila et al., 1984; Johannessen, 1991). In order to better understand its impact on the brain, especially in the context of apoptosis, oxidative stress and inflammation, the effects of UDCA in homeostatic state are also summarized. Overall, reported data showed that UDCA does not affect levels of oxidative stress and inflammation, but might regulate cell apoptosis in human brain blastoma cells to some extent.

Five studies showed that UDCA does not affect cell apoptosis in neurons (Rodrigues et al., 2000; Silva et al., 2001; Sola et al., 2006), astrocytes (Silva et al., 2001), human neuroblastoma cells (Chun and Low, 2012) and human glioblastoma cells (Yao et al., 2020). However, UDCA inhibits cell viability of glioblastoma multiforme, the most common and aggressive adult human brain cancer, in a dose- and time-dependent manner (Yao et al., 2020), and significantly increases the ratio of Bcl-2/Bax in human neuroblastoma cells after exposure to 200 μM UDCA for 12 h (Chun and Low, 2012). Additionally, UDCA increases ROS production in glioblastoma cells (Yao et al., 2020), while another *in vitro* study did not find significant changes in ROS production in human neuroblastoma cells (Chun and Low, 2012). In terms of inflammation, one *ex vivo* and one *in vitro* study showed that UDCA does not change levels of NO and IL-1β or inducible nitric oxide synthase (iNOS) production in rat primary microglial cells (Joo et al., 2003) and BV2 microglia (Joo et al., 2004).

### 4 Discussion

This review summarizes the effects of UDCA on cell apoptosis, oxidative stress and inflammation in the brain, across numerous models of neurodegenerative diseases, as well as in homeostatic states. Collectively, these findings indicate that UDCA exerts anti-apoptotic, antioxidant, and anti-inflammatory effects in specific models of PD, AD and HD. In particular, UDCA reduces cell apoptosis, prevents the production of ROS in MPP+ induced models and SNP-induced models, decreases TNF-α level in rotenone-induced models and Aβ-induced models, inhibits the production of IL-1β in LPS-induced models, and induces the apoptosis of brain blastoma cells in homeostatic conditions.

In Aβ-induced cell models of AD, UDCA prevents apoptosis from occurring (Sola et al., 2006) by inhibiting the production of pro-inflammatory cytokines and NO via deactivation of NF-κB (Joo et al., 2003, 2004). Although several pieces of evidence found that UDCA may have the capability of controlling NF-κB activation via a negative feedback mechanism (Joo et al., 2004), UDCA’s actual mechanism of regulating NF-κB signalling remains unclear in brain cells. However, studies in other cell lines have shown that UDCA targets
the ligand binding domain of the glucocorticoid receptor (GR) and thereby regulates GR-mediated suppression of NF-κB transcriptional activity (Miura et al., 2001). Moreover, UDCA were shown to be able to reach the nucleus of primary rat cortical neurons, which suggests that UDCA may also play a specific role within the nucleus to protect neurons against apoptosis (Sola et al., 2006). Therefore, it is possible that UDCA may regulate several apoptosis-related pathways by functional modulation of GR.

Despite three different challenges were used to induce PD models, all of them are involved in mitochondrial impairment in dopaminergic cells. Similar to the most frequently used toxin MPP+, rotenone is able to inhibit complex I of the mitochondrial electron transport chain (Greenamyre et al., 2010), application of low dose of rotenone leads to degeneration of dopaminergic neurons (Blesa et al., 2012); while SNP is a strong NO generator, which can cause mitochondrial dysfunction in dopaminergic cells (Zhang and Zhao, 2003). Interestingly, the beneficial properties of UDCA are somewhat partially mediated by preventing mitochondrial dysfunction (Abdelkader et al., 2016; Chun and Low, 2012; Qi et al., 2021). In particular, UDCA treatment modulates mitochondrial homeostasis perturbations caused by treatment with rotenone in the striatum of male rat (Abdelkader et al., 2016), and prevents mitochondria-dependent programmed cell death in both SNP-induced human neuroblastoma cells (Chun and Low, 2012) and MPP+-induced mice neuroblastoma cells (Qi et al., 2021).

As observed in PD, mitochondrial dysfunctions also play a vital role in the neuropathology of HD (Carmo et al., 2018). The modeling toxin 3-NP is a potent inhibitor of mitochondrial succinate dehydrogenase, and can result in oxidized proteins in the striatum and substantial loss of striatal neurons (Gao et al., 2015). The treatment with UDCA exhibited to prevent several apoptotic events by inhibiting depolarization of the mitochondrial membrane (Rodrigues et al., 2000). Although the mitochondrial-mediated mechanisms by which UDCA inhibits apoptosis in these neurodegenerative models is not fully elucidated, they are very relevant to understand how UDCA exerts its role in the context of neurodegenerative diseases.

Related to this, there are currently three ongoing clinical trials that are testing UDCA in PD or HD patients: the first study focuses on the safety and tolerability of this bile acid in patients with PD (Clinical Trials registration: NCT03840005), the goal of the second one is to assess whether UDCA can slow the progression of PD and ultimately relieve its symptomatology (Clinical Trials registration: NCT02967250), and the later third one is to measure the safety and tolerability profile of UDCA in subjects with HD as well as the pharmacokinetics of this compound in serum and cerebrospinal fluid at standard oral doses (Clinical Trials registration: NCT00514774) (Zangerolamo et al., 2021). The results of these trials will be the basis for further validation of the pre-clinical evidence in this review and will confirm the knowledge outlined on the beneficial role of UDCA in reducing or delaying the neurodegeneration in PD and HD.

Noteworthy, in homeostatic conditions, most studies have shown that UDCA does not affect cell apoptosis, oxidative stress or inflammation, especially when used within a certain concentration range (50–800 μM) (Chun and Low, 2012; Joo et al., 2003, 2004;
However, UDCA is able to induce the cell apoptosis in two different kinds of brain blastoma cells (Chun and Low, 2012; Yao et al., 2020). It is known that patients with glioblastoma is poorly responsive to conventional therapy (Otto-Meyer et al., 2020), what is encouraging is that UDCA inhibits glioblastoma cell viability in a dose- and time-dependent manner via partly targeting gene expression related to mitochondria and endoplasmic reticulum (Yao et al., 2020). In line with these two studies in brain blastoma cells, UDCA has also been shown to induce apoptosis of several cancer cell types. For example, UDCA inhibits proliferation through caspase-mediated apoptosis in oral squamous cell carcinoma (Pang et al., 2015), and induces apoptosis through a caspase-dependent and independent mechanism in hepatocellular carcinoma (Tsagarakis et al., 2010). To note that the dual pro-apoptotic and anti-apoptotic properties of UDCA represent the characteristic traits of bile acids (Goossens and Bailly, 2019). Although additional experiments are still required to confirm the anticancer activity of UDCA in the brain, it shows promise as a possible therapeutic agent for the treatment of human brain tumour.

5 Conclusion and perspectives

It has been well-documented that UDCA exerts anti-apoptotic, antioxidant and anti-inflammatory effects in pre-clinical neurodegenerative models, and might has pro-apoptotic properties in brain blastoma cells as well. However, there is a lack of comprehensive study on a single type of neurodegenerative models to have investigated the role of UDCA. This is a limitation for interpreting potential molecular mechanisms of UDCA in the context of neurodegeneration.

Future studies will be expected to determine the precise molecular pathways, for instance, to identify the receptor(s) of UDCA and signal transducer activated by this bile acid, that will be important for more clinical trials to be conducted in humans, and ultimately to develop new therapeutic strategies based on modulation of apoptosis, oxidative stress and inflammation in neurodegenerative process. In addition, it also could be considered as an adjuvant therapy in combination with a routine prescription to improve the treatment outcomes in neurodegenerative disorders. Furthermore, it would be intriguing to unravel novel roles of UDCA in treating other neurological diseases.

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Biography

Fei Huang I have always been interested in neuropsychopharmacology of traditional Chinese medicine (TCM). I graduated from Nanchang University in China with a Master’s degree in clinical pharmacology in 2011. Then I completed my Ph.D. in TCM at the Institute of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine in 2015, where I investigated the effect of Astragaloside IV on enhancing memory and regulating hippocampal synaptic plasticity and its potential mechanisms under the supervision of Professor Zhibi Hu (Academician of the Chinese Academy of Engineering) and Professor Xiaojun Wu. Since my post-doctoral period, I have been working on the anti-depressive effects of TCM, with a particular interest in bile acids, on regulating hypothalamic-pituitary-adrenal (HPA) axis and reducing inflammation. I became an associate professor in Shanghai University of Traditional Chinese Medicine in 2018. In order to deepen my knowledge in neuropsychopharmacology, I have been funded as a visiting researcher at King’s College London under the supervision of Professor Carmine M. Pariante and Dr. Borsini Alessandra, and at the same time I am completing another Master’s program on affective disorders. My current research in King’s College London continues with the potential effect of bile acids in neuropsychiatric disorders. I have been granted five funds from a range of organizations in China including the National Natural Science Foundation of China and the Shanghai Sailing Program for young talents in science and technology. In addition, I have over 40 publications, including six papers as the first author and fourteen papers as corresponding author. My expertise on neuropsychopharmacology spans pre-clinical models of neurodegeneration, neuroinflammation and stress, molecular mechanisms of cytokine action, protein quantification and gene expression analyses.

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