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Review

RIFAMPICIN: An antibiotic with brain protective function

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ABSTRACT

Besides its well known antibiotic activity rifampicin exerts multiple brain protective functions in acute cerebral ischemia and chronic neurodegeneration. The present mini-review gives an update of the unique activity of rifampicin in different diseases including Parkinson's disease, meningitis, stroke, Alzheimer's disease and optic nerve injury.

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1. Introduction

The overwhelming progress in basic neuroscience research led to many therapeutic advances for neurological diseases. Despite these achievements treatment opportunities for several diseases such as stroke or dementia are still devastating. Therefore, research focused on the development of novel candidates causally interacting in brain disease pathophysiology. Of these candidates, antibiotics are particularly interesting because they exert in addition to the substance immanent antibiotic activity an array of brain protective functions including the prevention of mitochondrial mediated cytochrome c release, microglial activation, glutamate neurotoxicity, and oxidative stress (Kim and Suh, 2009; Hashimoto, 2008; Mao, 2005; Rothstein et al., 2005; Tomiyama et al., 1996a). Rifampicin is a semisynthetic derivative of the rifampycins, a class of broad-spectrum antibiotics that are fermentation products of *Nocardia meditterranei*. The common structure of the rifampycins is a napthohydroquinone chromophore spanned by an aliphatic ansa chain (Tomiyama et al., 1996a). Rifampicin reaches maximal serum concentration in 1–4 h after application and its plasma half-time is 2–5 h (Acocella, 1978). The lipophilic ansa chain is mainly responsible for the transport of the drug across the blood-brain barrier (BBB) into the brain parenchyma (Mindermann et al., 1993). In the light

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of increasing evidences of oxidative stress and recently defined immunological cell death pathways in both acute and chronic neurodegenerative diseases the present review gives an update on the brain protective functions of rifampicin in the major diseases.

1.1. Stroke

Stroke is the third leading cause of death and adult morbidity in developed countries (Sudlow and Warlow, 1997; Rothwell, 2001). Many molecular mechanisms including the role of massive inflammation and oxidative injury have been proposed to explain the pathogenesis of this clinically devastating disease (Bowen et al., 2006; Dirnagl et al., 1999). Poststroke reperfusion leads to free radical accumulation and release which damages intracellular and extracellular membranes ultimately resulting in cell dysfunction and death.

This concept was confirmed by various studies establishing the neuroprotective efficacy of free-radical scavengers after cerebral ischemia (Hal et al., 1997). The structural feature of rifampicin suggests that this drug may function as a free radical scavenger with its naphthohydroquinone ring which may contribute to the function of a hydroxyl radical scavenger activities in inhibiting neurotoxicity (Tomiyama et al., 1996a; Hal et al., 1997). Furthermore, rifampicin has been shown to downregulate the expression of pro-apoptotic Bax and upregulate the expression of anti-apoptotic Bcl-2, Bcl-XL, and of anti-apoptotic gene products such as XIAP, cIAP2, FLIPs, which play essential roles to block ischemia-mediated cell death (Gollapudi et al., 2003; Kilic et al., 2004; Yulug et al., 2004; Yerramasetti et al., 2002). In this respect, we have earlier shown that rifampicin efficiently reduced brain injury and increased the number of viable neurons after permanent and transient focal cerebral ischemia in mice (Yulug et al., 2004). All these findings suggest that rifampicin may be particularly suited for the treatment of stroke, where both kinds of injury interfere or overlap with each other. Rifampicine may therefore be an ideal candidate because it counteracts infections in acute stroke and acts at the same time as neuroprotectant

1.2. Meningitis

Despite an effective antibiotic therapy, bacterial meningitis is still associated with high rates of mortality and permanent sequelae in children and adults. It is widely known that bacterial compounds release the production of reactive oxygen species (ROS), proinflammatory cytokines, excitatory amino acids and induce meningeal inflammation (Leib et al., 1996a,b; Mawatari et al., 1996; Tumani et al., 2000). Additionally, the functional relationship between oxidative injury and excitotoxicity has been established in several in vitro studies (Reynolds and Hastings, 1995). Radical scavengers were, for example, shown to attenuate early pathophysiological changes in bacterial meningitis (Koedel and Pfister, 1999; Böttcher et al., 2000). However, the inflammatory host response after initiation of therapy with antibiotics currently used for meningitis may contribute to early mortality and long-term sequelae in bacterial meningitis (Nau et al., 1999; Böttcher et al., 2000). Antibiotics can lead to the release of proinflammatory components of the bacterial cell wall into cerebrospinal fluid (CSF) during bacterial lysis which can secondary cause a burst of meningeal inflammation (Böttcher et al., 2000; Mustafa et al., 1989; Nau et al., 1997) and injury to the host including loss of membrane function, DNA damage, and cell death (Leib et al., 1996a; Koedel and Pfister, 1999; Böttcher et al., 2000). In this respect, both in vitro and in vivo studies have demonstrated that antibiotics that act by inhibiting protein synthesis, such as rifampin and rifabutin, release smaller quantities of lipoteiochic acids (LTA)/teichoic acids (TA) than b-lactam antibiotics (Nau et al., 1999; Stuertz et al., 1998).

Nau et al. compared by their interesting study the effects of rifampicin with those of ceftriaxone on mortality, neuronal damage, and LTA-TA concentrations in serum and CSF in a model of experimental meningitis in mice (Nau et al., 1999). After intracerebral infection with *S. pneumoniae* they applied 2-mg doses of rifampicin or ceftriaxone and demonstrated that rifampicin not only reduced overall mortality during the first 24 h but led to a significant decrease of serum and cerebrospinal fluid concentrations of proinflammatory bacterial compounds compared to ceftriaxone-treated mice. This study confirmes previous data from a rabbit model of pneumococcal meningitis comparing the effect of rifampicin versus ceftriaxone on ROS production of CSF phagocytes, on CSF malondialdehyde (MDA) concentrations, and on neuronal damage. The study suggests that CSF leukocytes from rifampicin-treated rabbits produced less ROS than leukocytes from animals treated with ceftriaxone (Böttcher et al., 2000). Böttcher et al. (2000) interestingly found that the CSF malondialdehyde concentrations and the density of apoptotic neurons in the dentate gyrus were lower after rifampicin than ceftriaxone-treated animals providing further evidence that minimizing the release of proinflammatory bacterial compounds may improve outcome in bacterial meningitis. Favoring the therapeutic role of antibiotics that do not interfere with cell wall synthesis, these findings were suggested with two earlier studies showing that rifabutin and quinupristin–dalfopristin inhibited the rise of tumor necrosis factor in CSF compared with ceftriaxone therapy (Schmidt et al., 1997; Trostdorf et al., 1999). This was suggested by recent human studies showing that intensified treatment with high dose rifampicin could be associated with better survival in patients with tuberculous meningitis (Alvares-Uria et al., 2013; Ruslami et al., 2013)

In conlusion, with its radical scavenging and immunomodulating efficacy, rifampicin represents an interesting therapeutic candidate for reducing early mortality in bacterial meningitis.

1.3. Optic nerve injury

Optic nerve injury models provide valuable opportunities to discover and study mechanisms of axotomy induced retinal ganglion cell apoptosis and allowed the evaluation of several potential strategies for neuroprotection in neurodegenerative diseases. It has been shown that transection of the optical nerve (ON) triggers a highly coordinated response of injury-associated genes, which finally leads to apoptosis of retinal ganglion cells (RGC) (Kilic et al., 2004; Isenmann et al., 1997; Klocker et al., 1998). In neurodegenerative disease, it is widely known that production of reactive oxygen species overwhelm endogenous antioxidant defense mechanisms hereby inducing neuronal cell death. In this respect, antioxidant agents were shown to suppress apoptosis induced by various insults, including axotomy (Kilic et al., 2004; Castagne and Clarke, 1996). The free radical–scavenger activity of rifampicin has been shown by electron spin resonance spectrometric analysis and stable free radical alpha, alpha-diphenylbeta-picrylhydrazyl (DPPH) reduction (Kilic et al., 2004; Karunakar et al., 2003; Namba et al., 1992). Beyond the antioxidative properties of rifampicin, several other neuroprotective mechanisms have been discussed. Gollapudi et al. (2003) who reported that rifampicin-mediated inhibition of apoptosis and activation of caspase-3 and capase-8 occurred at least in part via Glucocorticoid receptor (GR) activation. Additionally, it has been already shown that rifampicin may block programmed cell death through various pro- and anti-apoptotic proteins (Gollapudi et al., 2003; Kilic et al., 2004; Yulug et al., 2004; Yerramasetti et al., 2002). In the light of these findings, we have earlier evaluated the possible neuroprotective effect of rifampicin comparing the vehicle and rifampicin treated mice after axotomy of mice (Kilic et al., 2004). After continious administration of 5 mg/kg rifampicin during the subsequent 14 days of axotomy we have evaluated the