Neuropharmacology 73 (2013) 174–182

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Mini-review

Antibiotics acting as neuroprotectants via mechanisms independent of their anti-infective activities

Matthew L. Stock [a,1], Kara J. Fiedler [a,1], Sreemoyee Acharya [a,1], Jennifer K. Lange [b,1], Gregory S.A. Mlynarczyk [a,1], Stephen J. Anderson [c,1], Garrett R. McCormack [a,1], Sri Harsha Kanuri [a,1], Naveen C. Kondru [a,1], Matthew T. Brewer [a], Steve A. Carlson [a,*]

[a] Department of Biomedical Sciences, Iowa State University College of Veterinary Medicine, 2028 VetMed, Ames, IA 50011, USA
[b] Department of Kinesiology, Iowa State University College of Human Sciences, Ames, IA 50011, USA
[c] Department of Psychology, Iowa State University College of Liberal Arts and Sciences, Ames, IA 50011, USA

ARTICLE INFO

Article history:
Received 5 January 2013
Received in revised form
23 March 2013
Accepted 26 April 2013

Keywords:
Antibacterial
Antifungal
Neuroprotection

ABSTRACT

This review considers available evidence that some antibiotics have ancillary neuroprotective effects. Notably, β-lactam antibiotics are believed to increase the expression of glutamate transporter GLT1, potentially relieving the neurological excitotoxicity that characterizes disorders like amyotrophic lateral sclerosis. Minocycline has shown promise in reducing the severity of a number of neurological diseases, including multiple sclerosis, most likely by reducing apoptosis and the expression of inflammatory mediators in the brain. Rapamycin inhibits the activity of a serine/threonine protein kinase that has a role in the pathogenesis of numerous neurologic diseases. Herein we examine the unique neuroprotective aspects of these drugs originally developed as anti-infective agents.

1. Introduction

While the desired activity of an antibiotic is to kill or prevent the growth of offending pathogenic microbes, these drugs may also directly impact host factors that are not relevant to the infection being targeted. Adverse events are common to most antibiotics (such as gastrointestinal distress with any oral antibacterial drug) but certain antibiotics are associated with beneficial effects ancillary to the elimination of microbial pathogens (Table 1). Some ancillary effects are unique to a given antibiotic or antibiotic class, for example, alleviation of contracted tendons in horses by tetracyclines (Arnoczky et al., 2004), stimulation of gastrointestinal motility related to macrolides (Constable et al., 2012; Hawkyard and Koerner, 2007; Lam and Ng, 2011), and suppression of hyperadrenocorticism by azole antifungals (Behrend, 2006; Feelders et al., 2010). Anti-inflammatory effects have been associated with numerous antibiotics including β-lactams (Periti, 1998; Wei et al., 2012), dapsone (Gordon et al., 2012; Kast et al., 2012), fluoroquinolones (Blasi et al., 2012), griseofulvin (Ginsburg et al., 1987; Hussain et al., 1999), macrolides (Amsden, 2005; Cao et al., 2006; Corrales-Medina and Musher, 2011; Er et al., 2010), metronidazole (Rizzo et al., 2010), rifampicin (Gupta et al., 1975), and tetracyclines (Gordon et al., 2012; Moon et al., 2012). But perhaps the most remarkable ancillary effects are related to neuroprotection provided by certain antibiotics (Table 2). β-lactams are the model neuroprotective antibiotics, *i.e.*, their specific neuroprotective mechanism is universal within this class of drugs including the synthetic derivatives and even the β-lactamase inhibitors. In addition to inhibiting cell wall synthesis in bacteria, β-lactams also minimize the untoward excitotoxicity of glutamate, a common factor in an array of neurologic diseases (Bittigau and Ikonomidou, 1997; Hugon et al., 1996; Lau and Tymianski, 2010; Maragakis and Rothstein, 2001).

Two other important neuroprotectant antibiotics are minocycline, a synthetic tetracycline that acts as a neuroprotectant through anti-apoptosis and anti-inflammatory mechanisms (Plane et al., 2010), and rapamycin which is an anti-fungal agent with anti-apoptosis and pro-autophagy properties that provide neuroprotection (Bové et al., 2011). This review focuses on the clinical neuroprotection provided by β-lactams, minocycline, and rapamycin. These multi-purpose antibiotics represent harbingers of new therapies aimed at ameliorating neurologic diseases. This is especially true for β-lactams, which may become obsolete as antibiotics given the emergence of the New Delhi metallo-β-lactamases that inactivate all β-lactams except for the monobactams (Cornaglia et al., 2011).

* Corresponding author. Tel.: +1 515 294 0912; fax: +1 515 294 2315.
E-mail address: stevec@iastate.edu (S.A. Carlson).
[1] These authors had equal contributions.

0028-3908/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuropharm.2013.04.059

Table 1
Summary of the ancillary non-neuroprotective effects of antibiotics or classes of antibiotics. Each drug–disease combination with a unique mechanism is listed separately. *Histologic or morphologic outcomes are indicated in the absence of human data. **Collateral events from mTOR inhibition.

Antibiotic or antibiotic class	Disease/condition influenced by the ancillary effect	Therapeutic outcome(s)*	Proposed pathway(s) of the effect	References
Azole antifungals (least likely for itraconazole)	Hypercortisolemia	Reduces signs of hypercortisolemia by decreasing cortisol production	Inhibits steroidogenesis by blocking cytochrome p450 enzymes	(Behrend, 2006; Feelders et al., 2010)
β-lactam antibiotics	Inflammation	Anti-inflammation including anti-sepsis	Reduces cytokines	(Periti, 1998; Wei et al., 2012)
Clarithromycin	Neoplasia	Decreases tumor growth	Anti-angiogenesis	(Yatsunami and Hayashi, 2001)
Dapsone	Inflammation	Promotes healing of inflammatory dermatological lesions	Inhibits neutrophils, eosinophilic peroxidase, leukotriene B_4, and CD11B	(Gordon et al., 2012; Kast et al., 2012)
Doxycycline	Inflammation	Inhibits autoimmune neuritis	Decreases infiltration of macrophages and lymphocytes	(Yi et al., 2011)
Fluoroquinolones	Inflammation	Anti-inflammation	Attenuates cytokine response through a variety of mechanisms	(Blasi et al., 2012)
Griseofulvin	Inflammation	Reduces cell-mediated immunity in gout; curbs arthralgia and some dermatologic conditions	Inhibits leukocyte chemotaxis, IFα-induced HLA-dr expression, VCAM-1 expression, and PGE_2 expression	(Ginsburg et al., 1987; Hussain et al., 1999)
	Vasoconstriction	Increases blood flow in small vessels, especially against Raynaud's disease	Inhibits intercellular adhesion of vascular endothelial cells via VCAM-1	(Asahina et al., 2001; Creery et al., 1968)
Macrolides (including clarithromycin and roxithromycin)	Gastrointestinal ileus	Alleviates gastrointestinal stasis by enhancing gastrointestinal movements	Activates the prokinetic motilin receptor that couples to G proteins	(Constable et al., 2012; Hawkyard and Koerner, 2007; Lam and Ng, 2011)
	Inflammation	Inhibits periodontitis, and other types of inflammation	Inhibits MMPs, collagenases, and pro-inflammatory cytokines	(Cao et al., 2006; Er et al., 2010)
Metronidazole	Inflammation	Inhibits periodontitis	Inhibits the production of pro-inflammatory cytokines	(Rizzo et al., 2010)
Rapamycin	Organ transplantation	Prevents rejection of renal transplants	Inhibits T-cell activation and proliferation**	(Harrison et al., 2012; Morelon, 2001; Shafaeddin Schreve et al., 2012)
	Neoplasia (tuberous sclerosis and neurofibromatosis)	Decreases tumor growth	Interrupts cellular division at G1**	(Chan, 2004)
	Aging	Prolongs lifespan	Reduces rpS6**	(Harrison et al., 2009)
	Cardiovascular diseases	Prevents revascularization around stents	Interrupts cellular division at G1 to S transition in vascular smooth muscle, prevents cell cycle progression via p27kip1, decreases cardiomyocyte proliferation, and encourages autophagy**	(Adelman, 2010; Kushwaha, 2008)
Rifampicin	Inflammation	Anti-meningitis	Decreases prostaglandin E_2 production, inhibits T-cells via attenuated pro-inflammatory cytokine production, blocks degradation of inhibitor of NFkB, and inhibits phosphorylation of MAPKs	(Bi et al., 2011; Gupta et al., 1975; Spreer et al., 2009)
Roxithromycin	Neoplasia	Decreases tumor growth	Anti-angiogenesis	(Yatsunami and Hayashi, 2001)
Tetracyclines (1st generation)	Contracted tendons in horses	Induces ligament and tendon elongation	Decreases collagen gel contraction in myofibroblasts, and decreases MMP-1 production	(Arnoczky et al., 2004)
	Inflammation	Anti-respiratory endotoxicosis	Impairs neutrophil migration	(Gordon et al., 2012; Moon et al., 2012)