Experimental Neurology 224 (2010) 56–65

Contents lists available at ScienceDirect

Experimental Neurology

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

Review

The endocannabinoid system: A new entry in remote cell death mechanisms

M.T. Viscomi [a], S. Oddi [a,b], L. Latini [a], E. Bisicchia [a,b], M. Maccarrone [a,b,*], M. Molinari [a,*]

[a] Santa Lucia Foundation I.R.C.C.S., Via del Fosso di Fiorano 65, 00143 Rome, Italy
[b] Department of Biomedical Sciences, University of Teramo, 64100 Teramo, Italy

ARTICLE INFO

Article history:
Received 25 March 2010
Accepted 25 March 2010
Available online 29 March 2010

Keywords:
Axotomy
Neurodegeneration
NOS
Purinergic
Cerebellum
Apoptosis
Necrosis
Neuroprotection

ABSTRACT

Functional impairment after development of focal CNS lesions depends highly on damage that occurs in regions that are remote but functionally connected to the primary lesion site. These remote effects include cell death and structural changes, and they are important predictors of outcome in several pathologies, such as stroke, multiple sclerosis, and brain trauma. A greater understanding of the neuropathological mechanisms that exist in regions that are remote from focal primary lesions is therefore essential for the development of neuroprotective strategies.

Endocannabinoids constitute a novel class of lipids that regulate mammalian cell apoptosis and the pathogenesis of neuroinflammatory and neurodegenerative diseases. In addition to well-described pharmacological actions in the brain, such as analgesia, hypokinesia, and hypothermia, endocannabinoids have been recently reported to control neuronal cell fate in various neuropathological conditions. Following brain injury, endocannabinoids are released, causing both protective and degenerative effects. Several hypotheses have been proposed to explain their role, but the mechanisms by which they act are largely unknown. New evidence indicates that the endocannabinoid system is a key participant in the determination of cell fate in remote cell death and its associated mechanisms. This review addresses recent findings on endocannabinoid function, focusing particularly on the relationships between the nitrergic, purinergic, and endocannabinoid systems.

Contents

Introduction

After CNS lesions develop, degeneration occurs not only locally but also in regions that are remote, yet functionally connected, to the primary lesion site. Nevertheless, most studies on focal CNS injuries have analyzed the principal site of damage, neglecting remote degenerative events and considering them functionally irrelevant. In the 1990s, however, remote cell death was recognized to be highly influential in determining the overall clinical profile in many CNS

* Corresponding authors. M. Maccarrone is to be contacted at University of Teramo, Piazza A. Moro 45, I-64100 Teramo, Italy. Fax: +39 0861 266877. M. Molinari, Fondazione S. Lucia, Via Ardeatina 306, I-00179 Roma, Italy. Fax: +39 0651501679.
E-mail addresses: mmaccarrone@unite.it (M. Maccarrone), m.molinari@hsantalucia.it (M. Molinari).

0014-4886/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.expneurol.2010.03.023

pathologies, such as stroke, multiple sclerosis, and traumatic brain and spinal cord injuries (Binkofski et al., 1996).

That processes that potentially affect long-term outcomes might be active, distal to the primary lesion site, days or months after injury establishes a basis for the exploitation of neuroprotective drugs. Due to its importance in clinical outcome and drug development, several models of remote damage have been developed and studied (Viscomi et al., 2009a; Block et al., 2005; Bramlett and Dietrich, 2007). Axotomy-induced remote degeneration has been used widely, and cannabinoid-oriented drugs have been shown to regulate neuronal survival in this model (Viscomi et al., 2009a).

In this review, we will focus on the relationships between cannabinoids and death signaling pathways that determine remote cell death after focal CNS lesion development.

Immediate and delayed damage

The pathophysiological mechanisms that underlie the damage that occurs in the brain and spinal cord are distinguished into two classical categories: i) immediate or primary changes that are related directly to the pathological insult—e.g., physical forces due to trauma or lack of blood supply; and ii) delayed or secondary changes that, despite being induced by the primary lesion, evolve independently. Secondary changes are sustained by a cascade of events that are active not only locally but also in areas that are partially affected or unaffected by the primary damage. Several factors regulate secondary neurodegeneration, including etiology, excitotoxicity, inflammation, and oxidative stress, and various therapeutic approaches have been proposed (Guimaraes et al., 2009).

Mechanisms of secondary degeneration are not limited to the lesion site; they also exist in regions that are remote but functionally connected to the primary lesion site. Remote delayed phenomena are activated by death signals that originate from the primary lesion and are relayed to remote areas by damaged axons or by changes in neuronal activity, involving multiple noncontiguous sites (Block et al., 2005; Bramlett and Dietrich, 2007). This type of secondary degeneration has been termed “remote damage” or “remote cell death,” but it has been poorly described (Viscomi et al., 2009a). Remote damage has been observed after surgical and traumatic brain (Barron et al., 1973; Macchi et al., 1975) and spinal cord injuries (SCI) (Feringa et al., 1988), as well as in focal vascular lesion models (Iizuka et al., 1990; Dihne et al., 2002).

The clinical significance of axonal/remote damage has been recognized recently and reviewed (Block et al., 2005; Viscomi et al., 2009a). Although neurodegeneration following axonal damage and target deprivation has been studied for several decades in many animal models (Torvik and Skjorten, 1971; Armstrong et al., 1987; Gage et al., 1986; Ruigrok et al., 1990), the mechanisms of retrograde neurodegeneration of axotomized/target deprived neurons remain poorly understood (Martin et al., 2003; Martin et al., 1998; Kataoka et al., 1989).

Animal models of remote cell death

To determine the mechanisms of progressive neuronal injury and degeneration, animal models of axotomy and target deprivation in different systems have been studied for many years (Barron et al., 1967; Gage et al., 1986; Armstrong et al., 1987; Sofroniew and Isacson, 1988; Ruigrok et al., 1990; Al Abdulla and Martin, 1998; Buffo et al., 1998; Viscomi et al., 2004) (Table 1). Among experimental models of remote damage, hemicerebellectomy is an excellent paradigm, in which events that occur in areas far from, but functionally related, to the primary lesion can be unequivocally dissected (Viscomi et al., 2009a).

Surgical removal of the cerebellar cortex and nuclei damages olivary and pontine axons, and due to the involvement of the deep cerebellar nuclei, the inferior olive and pontine nuclei are deprived of cerebellar input. This type of lesion evokes extensive neuronal death in the pontine and olivary nuclei that progresses for approximately 2 months, after which the lesional olivary and pontine neuronal population is reduced between 5 and 15% of prelesion values (Fig. 1A) (Buffo et al., 1998; Viscomi et al., 2004).

During this time, precerebellar neurons generate heterogeneous responses to axonal damage. At any time, cells exist in early as well as late degenerative states. Because axonal damage is generated only at once, differences in cell degeneration profiles suggest that axotomy-activated retrograde signals are not strictly committed to cell death but rather are influenced by external modulation. Therefore, it is conceivable that intrinsic and environmental factors, possibly subject to pharmacological manipulation, intervene to favor survival or death.

Table 1
Remote cell death experimental models — selected references.

Optic nerve injury	Villegas-Perez et al. (1993). Berkelaar et al. (1994). Garcia-Valenzuela et al. (1994). Bien et al. (1999). Levkovitch-Verbin et al. (2000). Levkovitch-Verbin et al. (2001). Levkovitch-Verbin et al. (2003). Blair et al. (2005). Fitzgerald et al. (2009).
Spinal cord transection	Goshgarian et al. (1983). Feringa et al. (1988). Tetzlaff et al. (1994). Brook et al. (1997). Kobayashi et al. (1997). Novikova et al. (2000). Shibata et al. (2000). Liu et al. (2002). Kwon et al. (2002). Tobias et al. (2003); Kwon et al. (2004). Xu et al. (2005). Sasaki et al. (2006). Wannier-Morino et al. (2008). Sasaki et al. (2009).
Cortex ablation	Al Abdulla et al., (1998). Al Abdulla and Martin (1998). Al Abdulla and Martin (2002). Martin et al. (2003).
Cerebellar system damage	Ruigrok et al. (1990). Buffo et al. (1998). Florenzano et al. (2002). Viscomi et al. (2004). Viscomi et al. (2005). Viscomi et al. (2008a). Viscomi et al. (2008b). Viscomi et al. (2009a). Viscomi et al. (2009b).

Clinical evidence and relevance

Remote degeneration is a common phenomenon in clinical neurological practice that can be observed using modern imaging techniques. In patients who are affected by focal brain damage, magnetic resonance imaging (MRI) can document atrophy of selective noncontiguous, but functionally related, brain regions that are distal to the primary area of damage (Nakane et al., 1992; Nakane et al., 1997; Nakane et al., 2002; Uchino et al., 2006). Several weeks after middle cerebral artery infarction, computed tomography or MRI has shown progressive atrophy of the ipsilateral thalamus (Tamura et al., 1991; Ogawa et al., 1997; Nakane et al., 2002).

Further, secondary degeneration in the brainstem has been detected by MRI after cerebrovascular accidents (Uchino et al., 2006; Ziemus et al., 2007). These instances of delayed degeneration have been linked to antero- and retrograde degeneration, and are critical