Neuropharmacology 104 (2016) 255–271

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

Purines in neurite growth and astroglia activation

Claudia Heine*, Katja Sygnecka, Heike Franke**

Rudolf Boehm Institute of Pharmacology and Toxicology, University of Leipzig, Härtelstr. 16 -18, D-04107 Leipzig, Germany

ARTICLE INFO

Article history:
Received 6 August 2015
Received in revised form
14 October 2015
Accepted 18 October 2015
Available online 21 October 2015

Keywords:
Neurite growth
Axon growth
Purines
P2 receptors
Astrogliosis
Glial scar
Neuronal development
Regeneration

ABSTRACT

The mammalian nervous system is a complex, functional network of neurons, consisting of local and long-range connections. Neuronal growth is highly coordinated by a variety of extracellular and intracellular signaling molecules. Purines turned out to be an essential component of these processes. Here, we review the current knowledge about the involvement of purinergic signaling in the regulation of neuronal development. We particularly focus on its role in neuritogenesis: the formation and extension of neurites. In the course of maturation mammals generally lose their ability to regenerate the central nervous system (CNS) e.g. after traumatic brain injury; although, spontaneous regeneration still occurs in the peripheral nervous system (PNS). Thus, it is crucial to translate the knowledge about CNS development and PNS regeneration into novel approaches to enable neurons of the mature CNS to regenerate. In this context we give a general overview of growth-inhibitory and growth-stimulatory factors and mechanisms involved in neurite growth. With regard to neuronal growth, astrocytes are an important cell population. They provide structural and metabolic support to neurons and actively participate in brain signaling. Astrocytes respond to injury with beneficial or detrimental reactions with regard to axonal growth. In this review we present the current knowledge of purines in these glial functions. Moreover, we discuss organotypic brain slice co-cultures as a model which retains neuron-glia interactions, and further presents at once a model for CNS development and regeneration. In summary, the purinergic system is a pivotal factor in neuronal development and in the response to injury.

This article is part of the Special Issue entitled 'Purines in Neurodegeneration and Neuroregeneration'.

Contents

* Corresponding author.
** Corresponding author.
E-mail addresses: Claudia.Heine@medizin.uni-leipzig.de (C. Heine), Katja.Sygnecka@medizin.uni-leipzig.de (K. Sygnecka), Heike.Franke@medizin.uni-leipzig.de (H. Franke).

http://dx.doi.org/10.1016/j.neuropharm.2015.10.022
0028-3908/

Abbreviations

AC	adenylate cyclase
ADP	adenosine diphosphate
Akt	serine-threonine kinase Akt
ATP	adenosine 5′-triphosphate
BDNF	brain derived neurotrophic factor
Ca^{2+}	calcium
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
CNTF	ciliary neurotrophic factor
DRG	dorsal root ganglion
E	embryonic day
EGF	epidermal growth factor
ERK	extracellular signal regulated protein kinase
FGF2	fibroblast growth factor 2
GDNF	glial derived neurotrophic factor
GFAP	glial fibrillary acidic protein
GSK3	glycose synthase kinase 3
IL	interleukin
MAPK	mitogen-activated protein kinase
NGF	nerve growth factor
NT	neurotrophin
PC12	pheochromocytoma cells
PCL	'pre-conditioning' lesion
PFC	prefrontal cortex
PI3K	phosphatidylinositol 3-kinase
PNS	peripheral nervous system
STAT	signal transducer and activator of transcription
SVZ	subventricular zone
TBI	traumatic brain injury
TNAP	tissue-non-specific alkaline phosphatase
TNF	tumor necrosis factor
UDP	uridine diphosphate
UTP	uridine 5′-triphosphate
VTA/SN	ventral tegmental area/substantia nigra
VZ	ventricular zone

Purinergic substances:

2ClATP	2-chloro-ATP (P2Y receptor agonist)
2MeSATP	2-methylthio ATP (P2X/Y receptor agonist)
ADPβS	adenosine-5′-O-(2-thiodiphosphate) ($P2Y_{1,12,13}$ receptor agonist)
PPADS	pyridoxal-phosphate-6-azophenyl-2′,4′-disulphonic acid (P2X/Y receptor antagonist)
BzATP	2′(3′)-O-(4-benzoyl)benzoyl-ATP (P2X7 receptor agonist)

1. Introduction

The ubiquitous purinergic signaling molecule adenosine 5′-triphosphate (ATP) serves as a fast excitatory neurotransmitter and is relevant for neuron-glial and glial-glial communications in the central nervous system (CNS) (e.g. Araque and Navarrete, 2010; Burnstock, 2008; Pankratov et al., 2007; Verkhratsky et al., 2009). The extracellular nucleotides ATP and ADP exert their biological activity by their binding to purinergic receptors, which are divided into two classes. The first class comprises the ionotropic P2X receptor family (P2X1–7). P2X receptors are stimulated by ATP and they are channels for sodium (Na^+) and calcium (Ca^{2+}) ions. Secondly, there is the G protein-coupled P2Y receptor family ($P2Y_{1,2,4,6,11\text{-}14}$). Depending on the subtype, P2Y receptors are activated by ATP, ADP, UTP, UDP, NAD^+ or nucleotide sugars. The P2Y receptors are coupled to several intracellular signal transduction pathways, including (i) the phospholipase C (PLC) catalyzed inositol-phosphate (PI) formation and the resulting release of Ca^{2+} from intracellular stores ($P2Y_{1,2,4,6,11}$) and (ii) the inhibition of cyclic adenosine monophosphate (cAMP) formation ($P2Y_{12,13,14}$) (e.g. Abbracchio et al., 2009; Ralevic and Burnstock, 1998). The P2X/Y receptors are broadly distributed in both neurons and glial cells. Thus, they are involved in multiple physiological functions, and they are of pathophysiological significance (Franke and Illes, 2006; Khakh and North, 2012; Köles et al., 2011; Tozaki-Saitoh et al., 2011).

A number of data point to an essential role of purines acting as trophic factors in neuronal cell growth, development and regeneration (for review see Burnstock and Verkhratsky, 2010; Franke et al., 2012; Fumagalli et al., 2011; Zimmermann, 2011). Important aspects of neuronal development (when neurons establish precise connectivity patterns) and regeneration (e.g. following traumatic brain injury (TBI), traumatic spinal cord injury, and ischemia) are the formation and extension of neurites. Acute brain injury and neurological/neurodegenerative disorders result in a cascade of tissue responses leading to axonal degeneration, cell death, (astro)glial activation and/or glial scar formation. The failure of spontaneous regeneration of injured axons in the adult mammalian CNS in contrast to the peripheral nervous system (PNS) is of important clinical relevance. Persistent functional deficits are often the consequence of acute brain injury, although many of the affected neurons survive the traumatic event (Cui, 2006). Thus, it is of crucial therapeutic importance to elucidate the molecular mechanisms of the neuronal growth and regrowth during development and the regeneration after PNS injury to translate this knowledge to potent therapeutical approaches to enable neurons of the mature CNS to regenerate.

Neuronal growth and neurite guidance represent highly coordinated processes controlled by a variety of extracellular and intracellular signaling molecules. Opposing permissive and repulsive signals have been identified (Cui, 2006; Díez-Zaera et al., 2011; Sofroniew, 2015; Zhou and Snider, 2006). Besides neurotrophic factors and axon guidance molecules purines play essential roles in these processes. A general overview of growth-inhibitory and growth-stimulatory factors and mechanisms involved in neurite growth will be given in a first part of the present review. In the second part we focus on the role of purinergic signaling in neuronal development. The generation of the functional and fully-wired mature nervous system comprises (i) the proliferation of early progenitors, (ii) the migration and (iii) the differentiation into