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ScienceDirect
Neurochemistry International 52 (2008) 5–13
NEUROCHEMISTRY International
www.elsevier.com/locate/neuint

Extrasynaptic transmission and the diffusion parameters of the extracellular space

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Received 26 February 2007; accepted 10 April 2007
Available online 19 April 2007

Abstract

Extrasynaptic volume transmission, mediated by the diffusion of neuroactive substances in the extracellular space (ECS), plays an important role in short- and long-distance communication between nerve cells. The ability of a substance to reach extrasynaptic high-affinity receptors via diffusion depends on the ECS diffusion parameters, ECS volume fraction α (α = ECS volume/total tissue volume) and tortuosity λ (λ^2 = free/apparent diffusion coefficient), which reflects the presence of diffusion barriers represented by, e.g., fine astrocytic processes or extracellular matrix molecules. These barriers channel the migration of molecules in the ECS, so that diffusion may be facilitated in a certain direction, i.e. anisotropic. The diffusion parameters α and λ differ in various brain regions, and diffusion in the CNS is therefore inhomogeneous. Changes in diffusion parameters have been found in many physiological and pathological states, such as development and aging, neuronal activity, lactation, ischemia, brain injury, degenerative diseases, tumor growth and others, in which cell swelling, glial remodeling and extracellular matrix changes are key factors influencing diffusion. Changes in ECS volume, tortuosity and anisotropy significantly affect the accumulation and diffusion of neuroactive substances and thus extrasynaptic transmission, neuron–glia communication, mediator ''spillover'' and synaptic crosstalk as well as, cell migration. The various changes occurring during pathological states can be important for diagnosis, drug delivery and treatment.

Keywords: Diffusion; Extracellular volume; Tortuosity; Magnetic resonance

1. Introduction

The classical type of signal transmission results from the activation of receptors located on the postsynaptic membrane. However, the existence of frequent functional interactions between nerve cells without any morphological (synaptic) contacts, ''mismatches'' between release sites and the location of receptors and the widespread existence of high-affinity nonsynaptic receptors (Herkenham, 1987) led to the conclusion that nonsynaptic communication is an important alternative to signal transmission in the CNS. It was shown in the pioneering studies of Sylvester Vizi that in response to the activation of noradrenergic neurons, there was an α-adrenoreceptor-mediated inhibition of acetylcholine release form nearby cholinergic terminals (Vizi, 1972, 1974). His idea arose mostly from studies of the monoamine system showing an indirect influence between sympathetic and parasympathetic activity without any obvious contact (Paton and Vizi, 1969; Vizi, 1968, 1974). Later, it was found that nonsynaptic communication is not limited to only the vegetative system, but that it is also a quite general feature of the central nervous system. This phenomenon was termed extrasynaptic or volume transmission (Agnati et al., 1995; Fuxe and Agnati, 1991) and in the last decades has attracted more and more attention (Agnati et al., 1995; Fuxe and Agnati, 1991; Nicholson and Sykova, 1998; Sykova, 1997; Vizi, 1984, 2003; Vizi et al., 2004; Vizi and Labos, 1991; Zoli et al., 1999). Nonsynaptic communication between neurons or neurons and glial cells is achieved by the diffusion of neurotransmitters in the ECS, by the accumulation of ions in the ECS (Sykova, 2004a,b) or by diffusible signals, e.g., nitric oxide (Kiss and Vizi, 2001; Kiss et al., 2004; Vizi,

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doi:10.1016/j.neuint.2007.04.007

2000). While neurons can interact by both synaptic and volume transmission, communication between neurons and glial cells is almost exclusively limited to the diffusion of neuroactive substances and ions in the ECS. The ''awareness'' of glial cells about, e.g., current neuronal activity, is crucial for their role in ionic, pH and volume homeostasis and their modulation of synaptic transmission efficacy. Volume transmission acts over a time-scale of seconds or minutes, in both short and long distance modes, and despite various studies, its importance in modulating and mediating various functions is still not completely recognized. This type of communication provides a mechanism for synchronizing neuronal activity and information processing in functions, such as sleep, vigilance, hunger, chronic pain, emotions, behavior, learning, lactation, depression, balancing between the sympathetic and parasympathetic nervous systems and many other plastic functions of the brain (Sykova, 1997, 2004a,b; Vizi, 1980, 1984, 2000, 2003). Its underlying mechanism is the diffusion of neuroactive substances in the ECS, which therefore serves not only as the microenvironment of nerve cells but also as an information channel.

Neuroactive substances and ions may be released into the ECS by various mechanisms, including extrasynaptic release during excessive stimulation (amino acids), extrasynaptic vesicular release from neurons or axonal varicosities (neuropeptides or catecholamines), the reversal action of glial transporters for transmitters (glutamate, GABA, dopamine), ionic shifts from the intercellular to the extracellular compartment or by the release of gaseous transmitters, such as nitric oxide (Fig. 1). The selectivity of synaptic transmission and its high signal-to-noise ratio are ensured by the ensheathing of synapses by glial processes and the extracellular matrix (ECM), forming perineuronal nets (Celio et al., 1998). In contrast to these ''private'' synapses, the insulation of other types of synapses is insufficient to prevent the escape of mediators from the synaptic cleft and leads to synaptic spillover, especially during repetitive stimulation. Via diffusion, neurotransmitters, such as glutamate or GABA can thus reach receptors at neighboring synapses and affect the efficacy of transmission by an independent pathway. This heterosynaptic communication, called synaptic crosstalk (Asztely et al., 1997; Kullmann et al., 1996), plays a role, for example, during long-term potentiation and depression (LTP and LTD, respectively), during lactation or dehydration, where it can potentiate hormonal release (Oliet et al., 2001; Piet et al., 2004), or in the indirect modulation of the dopaminergic system by excitatory input (Kiss et al., 2004).

The astrocytic ensheathing of synapses is plastic and may change over either a short time-scale during neuronal activity (Hirrlinger et al., 2004) or over a long time-scale, e.g., during lactation (Theodosis and Poulain, 1993). Due to transport mechanisms on astrocytic processes, which are in close contact with a synapse, astrocytes may suppress or facilitate neuronal activity by neurotransmitter uptake or release (for review, see Haydon, 2001). The importance of glial cells for synaptic transmission is reflected in the model of a ''tripartite synapse''

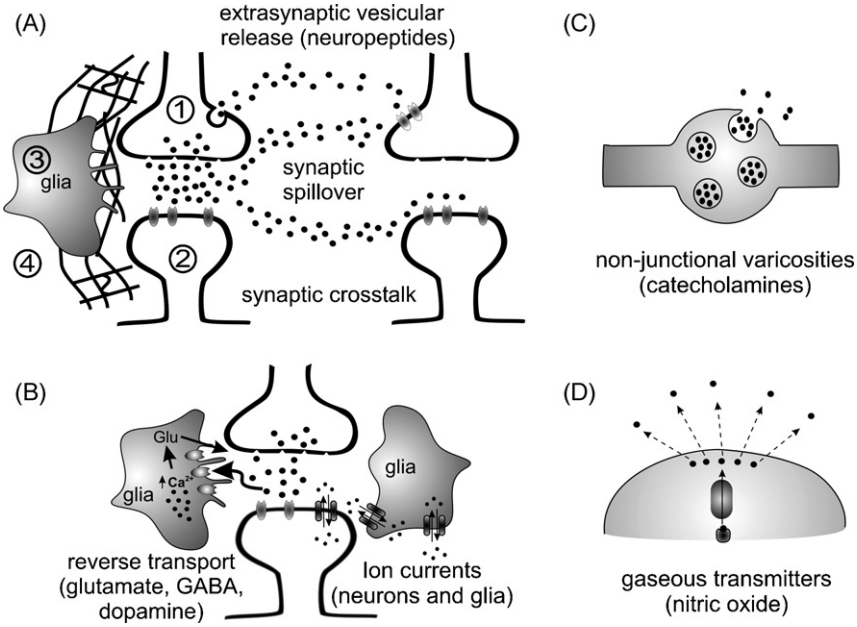

Fig. 1. Schematic representation of a quadripartite synapse (A) and the main sources of neuroactive substances involved in volume transmission in the extracellular space (ECS) (A–D). (A) Signal transmission is affected by four important elements: presynaptic terminals (1), postsynaptic terminal (2), glia and their processes ensheathing the synapse (3) and the extracelluar space (ECS) and its content, particularly the extracellular matrix (4). The main mechanisms responsible for the release of neuroactive substances into the ECS include: (A) vesicular release of transmitters either intrasynaptically followed by the diffusion of the transmitters outside the synapse – synaptic spillover and synaptic crosstalk (amino acids) or directly into the ECS – nonsynaptic release (neuropeptides); (B) the reverse functioning of transmitter uptake carriers (glutamate and GABA from astrocytes and glutamate and dopamine from neurons) and local ion currents induced by transmitter release (e.g., K^+) or by the activity of voltage-gated channels on neurons and glia; (C) vesicular release from nonjunctional varicosities during paracrine transmission (catecholamines); (D) the release of gaseous transmitters (nitric oxide from neurons and endothelial cells).