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Novel insights into gliotransmitters

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It is becoming increasingly clear that astrocytes play an active role in neural communications by releasing neuro-active gliotransmitters into extra-cellular spaces, where they act on neighbouring neurons in order to modulate synaptic transmission and plasticity, and affect behaviour. However, in terms of cell biology, our knowledge of the mechanisms governing the secretion of gliotransmitters is so much less detailed than our knowledge of those governing neurotransmitters that it has even been questioned whether astrocytes are capable of secreting molecules. This review critically evaluates the currently available findings concerning gliotransmitters with the aim of stimulating discussion in the field.

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Introduction

A nervous synapse is a miniscule gap across which the passage of chemical signals allows communication between one neuron and another. A great deal of information concerning synaptic structure, molecular components and physiological functions has been acquired over recent decades, and it is now known that synapses are crucial for brain functions such as behaviour, learning and memory [1].

Most of the brain disorders currently affect 1/3 of the population of industrialised countries [2] and are caused by synaptic dysfunctions. However, as neurons do not function in isolation but are part of an elaborate network in which they are intimately associated with glial cells, it is likely that the astrocytes contributing to the formation, function and plasticity of synapses are involved in the pathophysiology of various brain disorders, and may therefore be suitable diagnostic and therapeutic targets. Consequently, one of the most challenging tasks facing future research is to apply our growing understanding of 'tripartite synapses' (defined as the functional and structural integration of astrocytes and synapses) [3••] to developing new pharmaceutical and biotechnological means of controlling and restoring synaptic function.

The concept of 'tripartite synapses' arose from findings made by many laboratories during the 1990s that revealed the existence of bi-directional communications between neurons and astrocytes based on their respective release of chemical neurotransmitters and gliotransmitters [4,5]. This was a crucial advance in neuroscience because it indicated that astrocytes not only receive information from neurons, but could also potentially send signals back to neuronal networks. Over the last year the concept has evolved into the more generalised view of astrocytes modulating the extra-cellular spaces around synapses: that is 'an integrative functional view of synaptic physiology that considers astrocytes as active protagonists regulating information transfer between neurons' [3••]. The manner in which astrocytes influence synaptic physiology is multifaceted, and goes from providing structural support for the regulation of the components of extra-cellular space to neuromodulation (for reviews see [6–10]).

However, although there is no doubt about the role of perisynaptic astrocytes in the maintenance of extra-cellular ion and neurotransmitter levels by means of clearance mechanisms, their physiological ability to modulate synaptic activity by releasing neuroactive gliotransmitters has been questioned [11–13]. The aim of this review is to describe recent advances in our understanding of the physiological role of astrocytes and discuss the related controversial issues.

Are astrocytes highly secretory cells?

There is a growing consensus that astrocytes are highly secretory cells [9,14–17], and a number of families of astrocyte-released molecules have been identified. It has also been shown that they regulate various aspects of synaptic development and function under both physiological and pathological conditions, and this functional diversity suggests that they are involved in virtually everything the brain does. However, although it is generally accepted that astrocytes release many molecules, there is no agreement as to whether these also include neurotransmitters and neuromodulators.

On the basis of current opinion in the field, the substances released by astrocytes can therefore be divided into 'established' and 'emerging' substances (Table 1). The 'established' category mainly consists of those that are

Table 1

Emerging substances released by astrocytes

Substance	Mechanism(s) of release	Function	Ref.
Neurotransmitters			
Glutamate	Exocytosis[a,c] Plasma membrane channels: connexin (Cx) hemichannels Transporters: P2X7[a,c]; glutamate-cysteine antiporter[a,c] and excitatory amino acid transporters1/2 (EAAT1/2)[a]	Modulation of glutamate ionotropic and metabotropic receptors on neurons and glia[a,c]	[22,47–55,56••]
GABA	Plasma membrane channels: Best1 anion channel[a,c] Transporters: gamma-aminobutyric acid (GABA) GAT1 (SLC6A1) and GAT3 (SLC6A11) transporters[a,c]	Modulation of $GABA_A$ and $GABA_B$ receptors on neurons and glia[a,b]	[57,58]
Adenosine/ATP	Exocytosis[a,b] Plasma membrane channels: Cx or pannexin (Panx) hemichannels Transporters: P2X7 receptors ($P2X_7Rs$) and other anion channels[a,c,b]	Modulation of basal synaptic transmission by presynaptic A_{2A} receptor. It also has excitatory (P2X receptor) and pleiotropic effects (P_2Y) on neuron and glia cells[a,b]	[59–62]
Glycine	Transporters: glycine transporter GlyT1 (SLC6A9)	Inhibitory effects on neurons[a,b]	[69]
Neuropeptide Y	Exocytosis[a,c]	An important mediator of synaptic development and function	[32]
Neuromodulators			
D-Serine	Exocytosis[a,c] Plasma membrane channels: Panx hemichannels[a] and volume-regulated anion channels (VRCAs) Transporters: P2X7[a] and Na^+-independent alanine–serine–cysteine transporter-2 (ASCT2)[a]	Co-agonist of N-methyl-D-aspartate (NMDA) receptors. The release of D-serine from astrocytes is an important component of long term potentiation (LTP) in hippocampal Schaffer collateral-pyramidal neurons[a,c]	[63–68,96–98]

[a] In cultured cells.
[b] *In vivo*.
[c] In acute slices.

released on timescales ranging from minutes to days that regulate metabolism and the energy supply (including cerebral blood flow), inflammation and synaptogenesis. They therefore include metabolic substrates [18–21], eicosanoids ([22–26] and for review see [27]), scavengers of reactive oxygen species (ROS) [28], growth factors [29–31], hormones and peptides [32–35], synaptogenic factors capable of regulating synaptogenesis and synaptic connectivity [36–41], and pathologically relevant inflammatory factors [4,42–46]. The 'emerging' category consists of neuroactive substances, including neurotransmitters and neuromodulators, released on timescales ranging from milliseconds to minutes that can directly regulate synaptic transmission and plasticity by various mechanisms ([22,32,47–55,56••,57–69]; for reviews see [3••,9]).

It might be thought that this arbitrary classification would have been used to separate well-documented molecules from those still requiring more stringent level of evidence but, strangely enough, there is a lack of evidence in the case of the 'established' substances. For example, it is ostensibly widely accepted that synaptogenic factors (for review see [14]) affect synapse formation and maturation, but many of them have only been studied in cultured cells, and the cellular and molecular pathways governing their release (including whether the mechanisms are calcium-dependent) are still totally unknown (Table 2).

What is the reason for this biased acceptance accepting that astrocytes are highly secretory cells only in the case of a particular range of substances? The 'emerging' substances are in principle much more intriguing and, ever since their original description, gliotransmitters have received a great deal of attention because of their ability to interact with and modulate synaptic activity (for review see [4]), which strongly suggests the involvement of astrocytes in information processing, a function that was formerly reserved for neurons alone.

However, despite the considerable amount of experimental evidence accumulated over the last 15 years indicating that gliotransmitters play an active role in some forms of plasticity (for review see [3••,6,70••,71–75]), they are still the subject of much debate [11–13]. This is mainly due to the complexity of the cellular mechanisms governing their release and the effect of gliotransmission on synaptic activity. A number of unrelated laboratories have observed various calcium-dependent and calcium-independent mechanisms of gliotransmitter released by astrocytes under both physiological and pathological conditions, but