The astrogial endothelin system: toward solving a mystery
Focus on “Distinct pharmacological properties of ET-1 and ET-3 on astroglial gap junctions and Ca^{2+} signaling”

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The players within the astrogial endothelin (ET) system are known, but the rules of the game have been obscure... The current article in focus by Blomstrand and colleagues (Ref. 1, see page C616 in this issue) may shed some light on the physiological significance of the astrogial ET system.

Primary astrocytes in culture spontaneously express almost all constituents of the ET system, i.e., the peptides ET-1 and ET-3 (5, 18), the G protein-coupled receptors ETA and ETB (4, 11, 19), as well as ET-converting enzyme activity (2). Astrocytes in vitro, however, have always to be considered as being somewhat activated even under “basal conditions” compared with “resting astrocytes” in the brain. Accordingly, astrocytes in vivo express only low and hardly detectable amounts of the various components of the ET system in the “resting state” (6, 8, 16). This is markedly changed on activation as follows: after ischemia, neurotrauma, or inflammatory conditions of the brain, all components of the ET system are distinctly demonstrable in astrocytes both by in situ hybridization and immunohistochemistry (20). By this means, regional heterogeneity among astrocytes is found with respect to the ET system in vivo. Such heterogeneity can be confirmed in vitro and may reflect different functional requirements of distinct brain areas that become most obvious under activated conditions.

A particularly interesting aspect of ET biology is that the ET system can behave completely differently in different cell types. After neurotrauma, a downregulation of vascular ETB receptors resulting in a loss of ET-mediated vasodilation (9) is paralleled by a tremendous upregulation of astrogial ETB receptors (21). In this condition, the astrogial ETB receptors could serve as targets for the increased levels of ET-3, the endogenous ETB ligand. But brain injury increases ET-1 levels as well, and ET-1, although a potent nonselective agonist, binds to ETB receptors with similar affinity. What sense does it make to have both ET peptides around? The elevated levels of ET-1 and ET-3 may partly be derived from inflammatory cells but to a considerable extent also from astrocytes themselves. Why do astrocytes produce both peptides?

The work by Blomstrand et al. (1) may explain why and how the ratio of ET-1 to ET-3 can modulate astrogial function through subtle alterations of the Ca^{2+} signal pattern in single cells. In fact, ET-1 and ET-3 are shown by these authors to induce intracellular Ca^{2+} increases with different response patterns, while exhibiting comparable inhibition of gap junction permeability and comparable blockade of the propagation of intercellular Ca^{2+} waves in astrocytes. ET-1 and ET-3 thereby profoundly and variably influence astrocytic communication, ranging from cellular homeostasis to potential propagation of apoptotic signals (22). The types of ET binding sites involved as well as the ratio of extracellular ET-1 to ET-3 concentration may determine the relative amounts of cells displaying a certain Ca^{2+} signaling pattern. Variability of the Ca^{2+} signaling pattern in turn may be of major functional relevance, since this has been found to modulate efficiency and direction of gene transcription (3, 17). The interaction of both ETA and ETB receptors on astrocytes for creating a certain Ca^{2+} response pattern has also been demonstrated using cultures from ETB-deficient rats as a subtraction model (7).

How are differential effects of ET-1 and ET-3 achieved? Astrocytes express both ETA and ETB receptors. Although the effect of ET-3, a predominant ETB agonist, is entirely abolished by ETB antagonists, the action of ET-1 on astrocytes is by far more complicated. Only combined application of ETA and ETB antagonists is capable of measurably competing with ET-1, i.e., reducing or abolishing its effect in astrocytes, whereas each antagonist alone is inefficient. This has been observed in binding assays (12), ET elimination experiments (10), and, in the work of Blomstrand et al., both in gap junctional permeability and intercellular Ca^{2+} wave propagation experiments. This phenomenon could be explained based on the assumption that the ET-1 molecule can bind simultaneously to an ETA site and an ETB site. But how can such binding take place? A potential clue has been delivered by recent work on other G protein-coupled receptors, the γ-aminobutyric acid B (GABA_B) and the κ and δ opioid receptors. Heterodimerization is required for the formation of a functional GABA_B receptor out of per se nonfunctional GABA_B subunits (13, 15, 23). Heterodimerization, however, can also occur between two fully functional G protein-coupled receptors, as shown for the κ and δ opioid receptors (13).
opioid receptors (14), resulting in a “new” receptor with ligand binding and functional properties distinct from those of either receptor. Similarly, heterodimerization of ET_A and ET_B receptors in activated astrocytes may mediate functional diversity on stimulation. ET-3 would not be able to appreciably compete with ET-1 for binding to heterodimer receptors, whereas competition for binding to monomeric ET_B receptors between ET-1 and ET-3 would occur. Such “Lego-play” with receptor molecules may represent additional and as yet unrecognized instruments in a powerful concert of cellular interactions.

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REFERENCES

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