

LETTER TO THE EDITOR

POSSIBLE ROLE OF RECEPTOR PLASTICITY AND OF
NONSYNAPTIC DIFFUSION NEUROTRANSMISSION (NDN)
IN SHOULDER-HAND AND AUTONOMIC DYSREFLEXIA
SYNDROMES

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Recent evidence, and the re-interpretation of old experimental evidence, has led to the conclusion that nonsynaptic diffusion neurotransmission (NDN) mechanisms play a major role in information transmission in the normal brain.

In NDN (also called Volume Transmission: 1;12), neurotransmitters (e.g., dopamine, noradrenaline, serotonin and others) are released from vesicles outside the synaptic cleft, and reach receptors on the target cell surface by diffusing through the extracellular fluid; in the case of some neurotransmitters, such as nitric oxide and carbon monoxide, diffusion can also occur through the cell membranes (Fig. 1). Functions in which NDN mechanisms have been identified include: sleep, vision (at several levels from the retina to the visual cortex), long-term potentiation, and many others (1-6, 12). NDN may also be important in the recovery following brain damage (6, 7, 9), in spinal shock (8) and in pain (6).

Receptor plasticity refers to the change in the distribution of receptors to specific neurotransmitters, either at synapses or on the extrasynaptic cell membrane. An increase is called "up-regulation", while a decrease in receptors is called "down-regulation". Salpeter & Loring (16) have demonstrated the up-regulation of nicotinic acetylcholine receptors on the extra-junctional membrane of muscle fibers following damage to the innervating nerve, and the up-regulation of receptors on the extra-synaptic cell membrane may be a comparable response to damage in the central nervous system (CNS). De Keyser, et al. (10) demonstrated dopamine receptor up-regulation on the damaged side of human brains following unilateral massive brain stem stroke. The receptor plasticity (13) is a response to the decreased dopamine. The receptor

up-regulation may be on the extra-synaptic cell membranes, since virtually all the ascending dopamine fibers were destroyed by the stroke. Dopamine, as well as many other neurotransmitters, is found in the extracellular fluid (11, 18), which has been demonstrated to occupy approximately 20% of the brain (15). Thus, there is sufficient space for the neurotransmitters to be carried in the extracellular fluid to the cells (cf., 6).

The receptor up-regulation may increase the sensitivity of cells with altered innervation to specific neurotransmitters in the extracellular fluid. Evidence for extra-junctional release of noradrenaline (NA) has been assessed (9), and Stjärne (17) has reviewed the evidence for the extrajunctional release of adenosine triphosphate (ATP) as well as for the role of both NA and ATP in slow depolarization and slow excitatory junctional potentials (SJP) in the mammalian sympathetic nervous system. He noted that a neuropeptide such as neuropeptide Y (NPY) is also released during high frequency stimulation. Thus, the sympathetic nerve activity studied by him resulted from a combination of NA, ATP, and NPY activity; NDN is a factor in the action of each of those neurotransmitters (6). Comparable combinations have been demonstrated in the mammalian CNS (20). There is evidence that NPY is co-released with NA upon reflex sympathetic activation in man: under both surgical stress and vaginal delivery, as well as in physical exercise, the plasma levels of both NA and NPY increase (14). Vidal et al. (19) have implicated ATP release in an animal model of sympathetic system pathology: whereas ATP plays a negligible role as a mediator of vasoconstriction in the tail arteries of normal rats, it contributes markedly to vasoconstriction in spontaneously hypertensive rats.

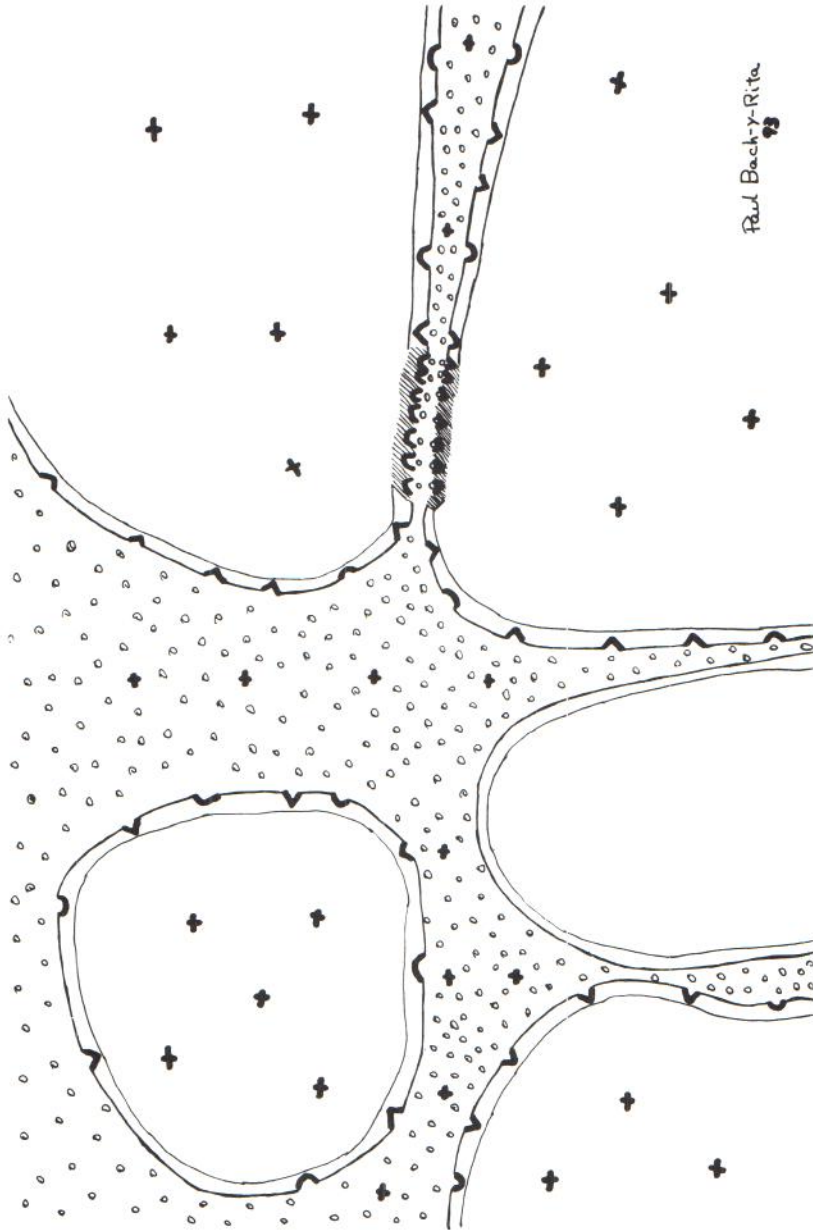


Fig. 1. A schematic slice through four neurons and a glial cell (upper left). Synaptic neurotransmission is shown in the shaded region between the two cells on the right, with neurotransmitter molecules (O) released from the upper cell reaching receptors (V) on the lower cell. Neurotransmitter molecules (from the neurons and the glial cell in the illustration, as well as from more distant cells out of the picture) are shown in the extracellular fluid bathing the cells. Each of the neurons and the glial cell have both extrasynaptic receptors (V) and extrasynaptic neurotransmitter release sites (U). The neurotransmitters (+) that diffuse across membranes as well as through the extracellular fluid are shown in both compartments. The cell in the lower middle is shown devoid of receptors, release sites or diffusible neurotransmitters. The cell in the lower middle is from one cell to diffuse past cells to activate more distant cells.

Receptor plasticity and NDN mechanisms comparable to those discussed above may play a role in shoulder-hand and reflex sympathetic dystrophy syndromes (6). Further studies are needed to specifically study this possibility.

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