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COMPARATIVE EFFICIENCY OF VOLUME AND SYNAPTIC TRANSMISSION IN THE COERULEAN SYSTEM: RELEVANCE TO NEUROLOGIC REHABILITATION

Paul Bach-y-Rita[1] and C. U. M. Smith[2]

From the [1]Department of Rehabilitation Medicine, University of Wisconsin Medical School, USA and the [2]Unit of Clinical Neurophysiology, Department of Vision Sciences, Aston University, UK

ABSTRACT. Over the past few years evidence has accumulated which confirms earlier beliefs that punctate synaptic transmission (wiring transmission) is not the only means by which "informational substances" affect cerebral neurons. This paper considers the relative efficiency of "volume" and "wiring" transmission in controlling large populations of neurons taking as a specific example the mammalian coerulean system. Making reasonable quantitative assumptions it is shown that volume transmission is a more efficient means of controlling "mass" functions than a wiring mode. Implications for the reorganisation of function following brain damage are noted.

Key words: volume transmission, coerulean system, locus coeruleus, reorganisation of function, brain damage.

Functions such as the individual finger movements of a pianist require high selectivity and rapid beginning and ending, such as occurs with synaptic action. In contrast, mass, sustained functions require massive activation, with less immediacy, and long maintenance, which can accommodate slow inactivation. We here discuss the comparative efficiency of volume and "wiring" (synaptic) transmission in the mass, sustained activity of the coerulean system. This system has been implicated in mechanisms of reorganisation of functions following brain damage (3, 7).

In volume transmission, Informational Substances (ISs) such as neurotransmitters, polypeptides, amino acids, may be released at points that may be remote from the target cells, which they reach by diffusion through the extracellular fluid to exert desynchronized and sustained influences on vast neuronal ensembles. Volume transmission has been called a ". . . complementary, if not alternative mechanism to classical chemical synaptic transmission . . ." (8) and has been implicated in mechanisms of re-organisation of brain function (2, 5).

A neurohumoral transmission mechanism by local diffusion had been proposed in 1964 by Bach-y-Rita (1) to account for the sustained activity recorded by him in highly convergent brain cells (i.e. cells responding to stimulation of several modalities from different parts of the body). However, further elucidation of the concept did not occur until receptor identification methods were developed. In a series of studies begun in 1968, Fuxe and his collaborators used monoamine fluorescence histochemistry to show extraneuronal fluorescence which they interpreted as the diffusion of monoamines in the extracellular space (12). This led them to propose a primarily non-synaptic information transmission mechanism for which they coined the term "volume transmission" (11).

Early receptor localization studies revealed evidence for volume transmission, but in the absence of an accepted conceptual framework for volume transmission, such evidence was ignored. A review of the evidence for discrepancies, or "mis-matches", between ISs and their receptors, which were initially considered to be exceptional instances, suggested to Herkenham (14) that, in the brain, mismatches are the rule rather than the exception. The initial studies demonstrating that the monoamine systems were highly non-synaptic (6) were challenged (17), but more recent immunostaining studies (9, 19) have confirmed the earlier radioautographic studies. In the presence of evidence for mis-matches and highly non-synaptic IS systems reflecting transmitter release from some point distant to the receptors, volume transmission should be considered as a significant mechanism of neuronal communication.

Evidence for volume transmission has recently been

reviewed (4, 11). Vertebrate and invertebrate studies have demonstrated communication by mechanisms that we have interpreted as volume transmission (2). Bach-y-Rita has evaluated the evidence for a role for volume transmission in the neural mechanisms of recovery from brain damage (2) and for a role in mass, sustained functions such as mood, sleep and wakefulness (3).

The locus coeruleus is a small (1650 nerve cell bodies in the rat (20)) pontine nucleus that spreads hundreds of millions of axon noradrenaline (NA) containing varicosities throughout every region and layer of the cortex; it has been implicated in numerous functions such as attention, arousal, sensory perception and memory. The varicosities rarely show a membrane differentiation characteristic of synaptic contact, and thus the cortical noradrenaline innervation is mostly (75–85%) non-junctional (19). Seguela et al. showed that the NA-immunostaining varicosities were most numerous in the molecular layer of the cortex where the coerulean fibres ran horizontally. It is likely, therefore, that the distal parts of cortical dendritic trees are a favored target for this system. Of the few junctional complexes formed by noradrenaline varicosities, 12 times as many were found on the dendritic shafts as on dendritic spines, while none were found on the cell body. Furthermore, cerebral astroglia possess non-synaptic receptors for ISs, including noradrenaline receptors (13), which provides another route whereby extrasynaptic ISs could provide a long-lasting effect on masses of neurons.

All of the factors mentioned above suggest that the coerulean system can influence a large volume of the cortex over a comparatively long period of time, and must be more efficient than a classical "wiring" system. Suppose some 10 000 coerulean fibres project to the cortex. What is the most efficient way these fibres could influence some 10^{10} cortical cells? Simple arithmetic shows that the wiring mode would require each coerulean fibre to provide 10^6 synaptic boutons on its telodendritic tree if the system were to innervate all the cortical cells and far more if the influence was to be powerful. Although these figures might be reduced if relay interneurons were involved, as in the basket cell system of the motor cortex (10), severe "packing" problems would occur in a space already devoted to complex cortical circuitry. It has been calculated that approximately 30 per cent of the volume of the mammalian cerebral cortex is taken up by axons (15). But, more significantly, a wiring mode would require continuous activity of coerulean fibres if the NA control was to be sustained and would consequently be energy inefficient.

Coerulean varicosities are generally not part of a junction, and so the released noradrenaline takes time to diffuse through the extracellular fluid (which constitutes approximately 20% of the living brain (16) to receptors. Changeux estimates the diffusion range (depending on the tortuosity (t)) to be several hundred microns (8). We have already noted that a preponderance of NA varicosities are located in the vicinity of the distant dendritic tree and thus, according to Rall's biophysics (18), the influence at the initial segment is maintained over a comparatively lengthy period. Moreover in the absence of a junction, inactivation of the noradrenaline is slowed: whereas conventional synapses have a full array of degradation enzymes and re-uptake mechanisms, non-junctional receptor sites possess few if any of these inactivating devices. Glial mechanisms provide still another mechanism for affecting the time course of noradrenaline activation. We conclude, therefore, that the effect of non-junctional noradrenaline is likely to be both more massive and longer lasting than a similar quantity of noradrenaline released at synapses.

Volume and synaptic transmission in the brain appear to be appropriate for distinctly different functions. Whereas synaptic (wiring) transmission is well adapted for the rapid control of reflex activity and the computations of neural nets, volume transmission provides an efficient mechanism for the coerulean and other systems to achieve widespread sustained influences including those that Bach-y-Rita & Bjelke (5) consider to be related to neurologic rehabilitation.

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Address for offprints:

Dr Paul Bach-y-Rita
Department of Rehabilitation Medicine
University of Wisconsin Medical School
Madison, WI 53792
USA