Journal of Physiology - Paris xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Modulatory compartments in cortex and local regulation of cholinergic tone

Jennifer J. Coppola [a,1], Nicholas J. Ward [a,1], Monika P. Jadi [b], Anita A. Disney [a,*]

[a] Department of Psychology, Vanderbilt University, PMB 407817, 2301 Vanderbilt Place, Nashville, TN 37240-7817, USA
[b] Computational Neurobiology Laboratory, Salk Institute for Biological Studies, 10610 North Torrey Pines Road, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:
Received 16 May 2016
Received in revised form 26 July 2016
Accepted 19 August 2016
Available online xxxx

Keywords:
Acetylcholine
Neuromodulation
Cortex
Compartments
Volume transmission

ABSTRACT

Neuromodulatory signaling is generally considered broad in its impact across cortex. However, variations in the characteristics of cortical circuits may introduce regionally-specific responses to diffuse modulatory signals. Features such as patterns of axonal innervation, tissue tortuosity and molecular diffusion, effectiveness of degradation pathways, subcellular receptor localization, and patterns of receptor expression can lead to local modification of modulatory inputs. We propose that modulatory compartments exist in cortex and can be defined by variation in structural features of local circuits. Further, we argue that these compartments are responsible for local regulation of neuromodulatory tone. For the cholinergic system, these modulatory compartments are regions of cortical tissue within which signaling conditions for acetylcholine are relatively uniform, but between which signaling can vary profoundly. In the visual system, evidence for the existence of compartments indicates that cholinergic modulation likely differs across the visual pathway. We argue that the existence of these compartments calls for thinking about cholinergic modulation in terms of finer-grained control of local cortical circuits than is implied by the traditional view of this system as a diffuse modulator. Further, an understanding of modulatory compartments provides an opportunity to better understand and perhaps correct signal modifications that lead to pathological states.

1. Introduction

Chemical signaling between neurons is often viewed as a relatively simple relationship in which an action potential in one neuron leads to signal transduction in another neuron. In classical synaptic transmission, action potentials travel to the axon terminal, where signaling molecules are released into the synapse, across which they will diffuse and subsequently bind to postsynaptic receptors, thereby transmitting a neural signal. This type of "point-to-point" transmission generally results in a signal that is both temporally and spatially precise.

Synapses open signaling to local modification. Here we argue that, in the case of diffuse communication by long-range neuromodulatory systems, there are many more opportunities to violate an assumption of a tightly coupled relationship between signal sent (by presynaptic neurons) and signal received (at postsynaptic neurons). In neuromodulatory systems signaling via non-synaptic transmission, mechanisms exist that can alter the coupling between action potentials (spikes) at the soma and the resulting response in local cortical circuits. Features such as patterns of axonal innervation, tissue tortuosity and molecular diffusion, effectiveness of degradation and reuptake pathways, subcellular receptor localization, and patterns of receptor expression across the local receiving circuit can offer the capacity to locally modify long-range communication between neurons.

Signaling by neuromodulators is generally considered broad in its impact, creating a neuromodulatory "tone" across large regions of the cortex. In much of the literature exploring the spatial and temporal scale of modulatory signaling, there is an implicit assumption that the number of neurons in the innervating modulatory structure defines a lower limit on the size of a uniquely modulated compartment in cortex. Here, we argue that local characteristics of cortical circuits can loosen spike-response coupling and introduce locally specific responses to broadcast modulatory signals, thereby creating small modulatory compartments in cortex without increasing neuron numbers in subcortical structures. We further argue that the signaling between these modulatory compartments can vary considerably and that these local

* Corresponding author.
E-mail addresses: jennifer.j.coppola@vanderbilt.edu (J.J. Coppola), nicholas.j.ward@vanderbilt.edu (N.J. Ward), jadi@salk.edu (M.P. Jadi), anita.disney@vanderbilt.edu (A.A. Disney).
[1] Authors contributed equally to manuscript.

http://dx.doi.org/10.1016/j.jphysparis.2016.08.001
0928-4257/

compartments have the ability to regulate their own modulatory input leading to a two-way, interactive communication. As such, the circuit itself can influence the modulatory signals that regulate its activity.

Acetylcholine (ACh) acts a neuromodulator in cortical circuits and is believed to support cognition. Its role in the central nervous system is still poorly understood, although it has been implicated in many processes including learning, memory consolidation (reviewed by Hasselmo and McGaughy, 2004), arousal (Jasper and Tessier, 1971), and attention (reviewed by Everitt and Robbins, 1997; reviewed by Sarter et al., 2005). We argue that anatomical differences across cortex that constrain and shape the way ACh interacts with local cortical circuitry result in the capacity for these circuits to regulate their own cholinergic modulatory tone, resulting in distinct "cholinergic compartments" across cortex. Furthermore, the existence of these compartments calls for thinking about cholinergic modulation in terms of finer-grained control of local cortical circuits than is implied by the traditional view of this system as a diffuse and loosely topographic modulator. These compartments are not limited to traditionally defined cortical areas, or even anatomically or functionally defined subregions within cortical areas, but comprise any region of cortex over which modulatory conditions are relatively uniform. Additionally, these compartments provide a substrate for an interactive relationship between cholinergic inputs and task-relevant cortical circuitry. This configuration allows for task-relevant circuitry to "demand" its own modulation, which prompts a cholinergic "response." The following review emphasizes evidence from studies of the macaque monkey. However, when data regarding primates are not available, or when notable species differences exist, we include information from other model systems.

2. Volume transmission

Classical synaptic transmission provides one mechanism for chemical signaling between neurons. Non-synaptic transmission, often termed "volume" transmission is another method by which cells communicate. This term, introduced by Fuxe and Agnati (1991), describes the diffusion of signaling molecules throughout the extracellular space, beyond the confines of a synapse (Fig. 1). Many neuromodulatory molecules are thought to signal, at least in part, through volume transmission. This type of communication differs from classical synaptic (point-to-point) transmission (Fig. 1A) in that molecules are released from varicosities that are not apposed to a specialized receptive surface (Fig. 1B). Under these circumstances, it is often thought that the resulting signal will be both slow and homogeneous over large regions of cortex. This is in contrast to classical synaptic transmission in which signals are generally assumed to be fast and precise. Here, we challenge this simple dichotomy. We offer a new interpretation of volume transmission in which modulatory signals have the capacity for higher spatial and temporal precision—conferred by features of local cortical compartments—than has traditionally been assumed. This likely results in the capacity for a spectrum of signaling precision that varies across time and differs over the space of the cortical mantle, possibly on a very fine scale.

In volume transmission, signaling molecules are thought to diffuse away from a release site and bind to receptors over some volume of tissue. Volume transmission can also occur when molecules released into a synapse spillover, outside of the synapse, and subsequently bind to nearby non-synaptic receptors. All chemical communication between cells provides an opportunity for a signal to be modified. In volume transmission, however, there is a greater opportunity for signal modification as a result of the time and distance over which the modulatory molecule is able to diffuse. That is, local features of the receiving circuit have the ability to influence cortical modulation, both across and within regions. For example, ACh is synthesized by neurons in the basal forebrain, which provides the only source of cortical ACh in adult primates (Mesulam et al., 1983). It is released from axonal varicosities to bind to receptors that are usually not associated with synaptic specializations (Umbriaco et al., 1994; Mrzljak et al., 1995; but see Turrini et al., 2001). However, despite all of neocortex receiving ACh from the same subcortical nuclei, differing patterns of axonal innervation may provide varying levels of ACh to each area. The cholinergic innervation of cortex in macaques (Mesulam et al., 1983) and humans (Mesulam, 2004) exhibits a broad topography based upon the projections from subdivisions of the basal forebrain. Raghanti et al. (2008) have shown that the density of this cholinergic innervation differs on a finer scale between Brodmann areas 4, 9, and 32 in the frontal lobe of the macaque. Dense networks of cholinergic axons are likely to yield a higher density of release sites and thus more ACh being delivered to an area.

Axonal innervation of the cortical mantle by cholinergic neurons exhibits still finer grained laminar differences within a single cortical area. In macaque frontal area 46, the supragranular layers I, II, and superficial III show denser patterns of cholinergic axons than the infragranular layers (Mrzljak et al., 1995), again suggesting the supragranular layers will be exposed to high levels of extracellular ACh. These studies provide evidence that while all ACh release across cortex is provided by a relatively small number of neurons in the basal forebrain, the signal received in a patch of cortex may vary as a result of differences in the density of cholinergic innervation.

In addition to differences in the density of cholinergic innervation, local regulation of ACh synthesis can influence the capacity

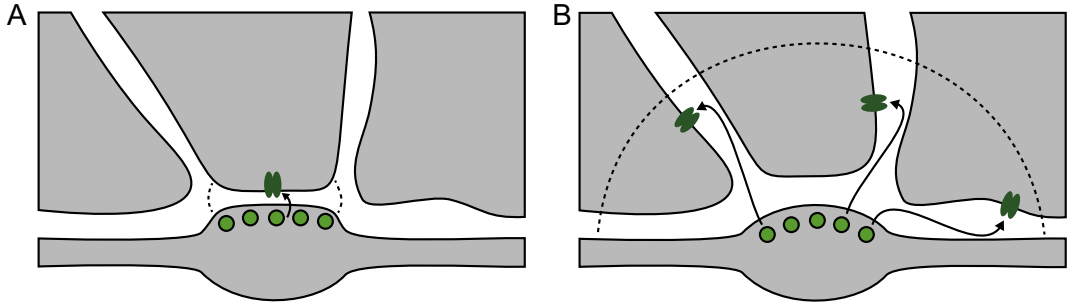

Fig. 1. Synaptic and non-synaptic "volume" transmission. Examples show an axonal varicosity releasing signaling molecules. *A* demonstrates classical synaptic transmission, in which molecules (shown in light green) released from the varicosity cross the synapse and bind to a receptor (shown in dark green). *B* demonstrates the release of molecules into a volume of tissue that diffuse away to bind to nearby receptors. Dashed lines indicate the extent to which molecules will diffuse in each type of transmission. Arrows indicate paths of molecular diffusion through the extracellular space toward receptors.

Please cite this article in press as: Coppola, J.J., et al. Modulatory compartments in cortex and local regulation of cholinergic tone. J. Physiol. (2016), http://dx.doi.org/10.1016/j.jphysparis.2016.08.001