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Review

Regulation of cortical acetylcholine release: Insights from in vivo microdialysis studies

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ABSTRACT

Acetylcholine release links the activity of presynaptic neurons with their postsynaptic targets and thus represents the intercellular correlate of cholinergic neurotransmission. Here, we review the regulation and functional significance of acetylcholine release in the mammalian cerebral cortex, with a particular emphasis on information derived from in vivo microdialysis studies over the past three decades. This information is integrated with anatomical and behavioral data to derive conclusions regarding the role of cortical cholinergic transmission in normal behavioral and how its dysregulation may contribute to cognitive correlates of several neuropsychiatric conditions. Some unresolved issues regarding the regulation and significance of cortical acetylcholine release and the promise of new methodology for advancing our knowledge in this area are also briefly discussed.

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1. Introduction

It has now been roughly a century since the identification of acetylcholine (ACh) as a neurotransmitter in the mammalian central nervous system, and some six decades since Richter and Crossland published their findings on the relationship between physiological state and brain ACh content [126]. With the advent

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of the cortical cup and push–pull cannula techniques in the 1960s and 1970s, investigators were able to go beyond post-mortem measurement of ACh content and directly measure levels of this neurotransmitter in the living brain. It was the introduction of modern in vivo microdialysis and its widespread application beginning in the 1980s, however, which revolutionized our understanding of the physiological, pharmacological and behavioral mechanisms underlying ACh release. For example, early studies on the relationship between anesthesia and brain ACh content generally large increases peaking when the animal was sacrificed 30–60 min post-anesthesia (e.g. [40]). The first microdialysis studies using the same or similar anesthetics showed virtually the opposite effect—i.e. anesthetics produce a rapid decrease in brain ACh efflux (e.g. [75]). While the original studies may have correctly interpreted their results—that anesthesia increased post-mortem brain ACh content by inhibiting its 'liberation', in vivo microdialysis was important in eliminating a significant intervening level of inference between ACh measurement and the phenomenon of interest—the effect of a manipulation on ACh release. The improved temporal and spatial resolution of microdialysis over its predecessors, and its ready applicability to awake, behaving animal models converged with clinical literature on the postulated role of the cholinergic system in several neurodegenerative and neuropsychiatric conditions. This combination of factors led to a rapid increase in studies using microdialysis to study ACh release in the mammalian brain (Fig. 1).

Thus, ACh release has been measured using a variety of techniques in numerous parts of the central nervous system, with the functional significance of that dependent variable inferred on the basis of the anatomical source of ACh, the brain region where it is being measured, and the pharmacological or behavioral independent variable employed to invoke (or inhibit) release. The reader is referred elsewhere for a more exhaustive overview of all of these factors [121], which is far beyond the scope of this review. Rather, this paper will focus primarily on studies of ACh release in the mammalian cerebral cortex. Furthermore, because much of what we know about the nature of cortical ACh release has derived from in vivo microdialysis studies over the past two decades, this will form the basis for much of this review. Finally, we will conclude with a brief discussion of some current issues in the field of cortical ACh release and how they may be resolved by the next generation of tools for the measurement of cortical ACh release.

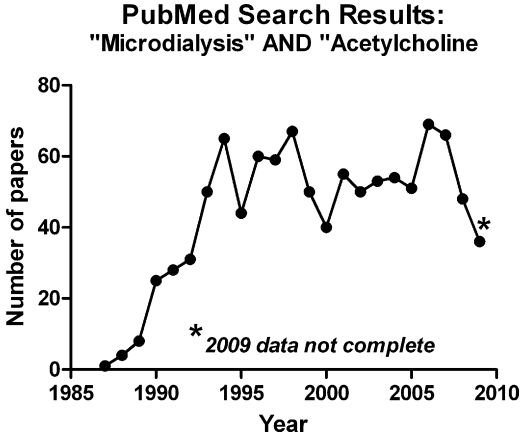

Fig. 1. Graph showing the number of papers published over the last 25 years using the search terms 'acetylcholine' and 'microdialysis' as indexed in the U.S. National Library of Medicine's PubMed online (www.ncbi.nlm.nih.gov/pubmed). The figure charts the appearance of microdialysis as a tool for the measurement of in vivo acetylcholine release in the 1980s followed by a rapid increase in the early 1990s and leveling off in the latter half of that decade. *Although 2009 data were not yet complete as of this figure, an apparent current downward trend may reflect the emergence of alternative, biosensor-based approaches with enhanced spatial and temporal resolution.

2. Microdialysis measurement of ACh: release versus efflux

ACh release represents the presynaptic component of endogenous cholinergic neurotransmission in the brain. ACh release follows a series of presynaptic electrical and signaling cascades (including sodium channel-dependent depolarization and calcium-dependent vesicular docking) culminating in the quantal elevation of synaptic ACh concentrations. Efflux, as measured extrasynaptically by *in vivo* microdialysis is a dependent measure reflecting a summed correlate of release, degradation and diffusion. While release and efflux represent different concepts, and in some cases can be dissociated experimentally (e.g. cholinesterase inhibitors may increase efflux while decreasing release), the terms are often used interchangeably. In this sense extracellular ACh measurement by microdialysis is analogous to an echo—temporally and spatially removed from the original sound but still, ideally, conveying a coherent enough signal to allow discernment of the 'message'. Because release is a component of efflux, and because release is generally the phenomenon of primary interest in microdialysis studies, we will primarily use this term for the purposes of this review, while acknowledging the aforementioned caveats.

2.1. Regulation of cortical ACh release by presynaptic mechanisms

While the bringing together of acetyl coenzyme A and choline in a reaction catalyzed by the enzyme choline acetyltransferase (ChAT) is the rate-limiting step in ACh *synthesis*, the rate-limiting factor in ACh *release* appears to be the availability of presynaptic choline via sodium-dependent high affinity choline transport [77,107]. Transgenic mice with up to 50% reductions in brain ChAT activity can maintain normal brain ACh content and depolarization-evoked ACh release by compensatory increases in choline transporter activity [16] and animals performing cognitive tasks can show up-regulation of cortical high-affinity choline transport [159], indicating that the choline transporter represents a plastic mechanism for responding to demands on the cholinergic system under pathological or normal conditions. Indeed, rapid insertion of vesicle-associated choline transporters into the presynaptic membrane may allow for maintenance of cholinergic capacity during periods of high or sustained cognitive activity [132].

ACh release, in addition to its dependence on high affinity choline uptake, is under most experimental conditions also highly dependent on local depolarization. Administration of the voltage-gated sodium channel blocker, tetrodotoxin, via the microdialysis probe generally reduces extracellular ACh levels by greater than 95% within 15–30 min, even under conditions of cholinesterase inhibition [44,102]. Thus, the ACh measured by the microdialysis technique is uniquely of neuronal origin and dependent on local action potentials.

3. Regulation of cortical ACh release by basal forebrain afferents: linking function with anatomy

Mammalian forebrain cholinergic neurons have been broadly grouped into four clusters, using the nomenclature of Mesulam et al. [94]: the first three subgroups (Ch1-3) consist of neurons in the medial septum and vertical and horizontal limbs of the diagonal band of Broca, and provide cholinergic innervation of the hippocampus and olfactory bulb. While some reports in rodents suggest that a portion of cholinergic innervation of the medial prefrontal cortex additionally arises from the diagonal band and medial septum [38,80], it is the Ch4 subgroup, consisting of a continuum of magnocellular, ChAT-positive neurons

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