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THE ROLE OF CHOLINERGIC SYSTEM IN NEURONAL PLASTICITY: FOCUS ON VISUAL CORTEX AND MUSCARINIC RECEPTORS

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INTRODUCTION

This review is focused on the basal forebrain (BFB) cholinergic system, cholinergic receptors and cholinoceptive target areas such as the neocortex, all of which are intimately involved in high cognitive functions and synaptic plasticity. The neurons of the BFB synthesize acetylcholine (ACh) whose action is mediated by two subclasses of receptors, namely nicotinic and muscarinic receptors. Using the visual system as a model, the aim here is to integrate and discuss the current knowledge on anatomy, ontogeny and function of the BFB cholinergic system. This signaling system represents the anatomo-functional basis of ACh action on neuronal network, neuronal plasticity and cognitive functions. Cholinergic system role on higher brain functions has received increasing attention since the first observation of A. Alzheimer (1907) reporting dramatic changes of the BFB cholinergic neuro-anatomy in one of the most devastating neurodegenerative diseases of adult brain, i.e. Alzheimer's disease (AD). In addition to this observation, later work demonstrated its participation in deep re-arrangements of brain connectivity such as the regulation of neuronal plasticity during maturation of cortical sensory maps, in adult and aged brain.

BASAL FOREBRAIN CHOLINERGIC SYSTEM

Cholinergic neurons of BFB include a series of small contiguous or interconnected groups of cells with similar properties in mammalian animal species; cholinergic nuclei project topographically to cholinoceptive target areas. For example, in rodents the nucleus basalis magnocellularis (NBM) is the equivalent of Meynert nucleus in the primates and send projections to several areas including cerebral cortex and amygdala while the innervation of hippocampus is provided by the medial septum-diagonal band complex (MS-DB) (45, 120).

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In addition to cholinergic neurons, in the BFB region there are other projecting neurons synthesizing different neurotransmitters such as gamma-aminobutyric acid (GABA; [54]). Rye *et al.* (145) showed that 30% of the BFB neurons projecting to the cortex are cholinergic. GABAergic neurons are intermingled with the cholinergic neurons in the BFB region and account for another 30% (55, 110).

1. *Anatomy*.

In the rat, BFB cholinergic neurons spread from the anterior medial septal nucleus to the rostral portion of the lateral hypothalamus caudally. The BFB cholinergic neurons are from medium to large sized, long axoned, and multipolar. Most of the cell bodies have an oval or fusiform shape. They display intense immunoreactivity for acetylcholine esterase (AChE), choline acetyltransferase (ChAT), and vesicular acetylcholine transporter (VAChT), as well as staining for ChAT and VAChT mRNA (151, 82). Based on specific projection areas, the BFB cholinergic neurons in rat give rise to at least four different pathways: 1) the basalo-olfactory bundle, projecting to the olfactory bulb and associated nuclei; 2) the basalo-hippocampal bundle originating in MS-DB and innervating the hippocampal formation and nearby limbic cortex; 3) the medial cortical pathway, originating mainly in the vertical and horizontal limbs of DB, NBM, and partially in the magnocellular preoptic area and substantia innominata. These nuclei project to medial cortical regions, including the medial frontal, cingulate, retrosplenial and medial occipital cortices; 4) the lateral basalo-cortical and basalo-amygdala tracts, supplying afferents to the remaining allocortex, to the lateral isocortex, and to the amygdala (16, 151). It is proposed that cholinergic neurons in the BFB provide the majority of the cholinergic innervation to the telencephalon (145).

In addition, intrinsic cortical cholinergic neurons characterized by a bipolar shape have been described in different mammalian species such as the rat, although the real cholinergic nature and function of these cells are still debated (78, 44, 108, 165).

The BFB cholinergic system is typically defined as a diffusely projecting system since almost all brain areas receive a cholinergic projection from it. However, cholinergic projections innervate relatively small regions, especially in sensory cortical areas. The sensory cerebral cortices can be divided into cytoarchitectonic regions that are constrained by the sensory modality of their thalamic inputs, and in turn each sensory modality is organized in a point to point representation. These modules are innervated by discrete groups of cholinergic cells residing in BFB region. Thus, activation of discrete cholinergic groups of neurons may induce functional changes in their respective sensory modules in the neocortex.

Cortical cholinergic varicosities have been described diffusely throughout different cortical layers. Remarkably, only a small fraction of ACh varicosities in the cerebral cortex displayed membrane synaptic specialization (164, see [35]). Specifically in the rat parietal cortex at postnatal day 38 (P38), i.e. at an age when the cholinergic fibers have already assumed an adult-like shape, synaptic junctions represent only 17% of whole varicosities (118). Usually, symmetric cholinergic synaptic contacts are primarily made with dendritic branches and less frequently with spines and cell bodies of either glutamatergic or GABAergic neurons (168, 79). On the other hand most of the cholinergic varicosities terminate free in the extracellular matrix without being associated with any synaptic specialization (164, 124). Non-synaptic varicosities seem to be randomly distributed in rela-

tion with the surrounding elements and show an incessant movement of translocation and re-shaping along the fibres (36). This motility may constantly modify the exact position of ACh releasing sites in relationship to the targets and hence their functional influence. Such characteristic suggests that ACh may act in a paracrine fashion on cortical elements, with ACh diffusing to the extracellular space and then influencing a large number of cortical elements (36). This modality of release is consistent with the concept of volume transmission of neurotransmitters proposed by Fuxe and Agnati (61). The concept of volume transmission is supported by the evidence of a small number of BFB projecting cholinergic neurons compared with that of cortical neurons subjected to cholinergic modulation (120).

Cholinergic nuclei receive afferent inputs from the cortex, striatum, hypothalamus and brainstem (152, 153, 32, 75; for a review see [146]). Afferent projections can be classified according to the neurotransmitter that is being released and these are basically glutamate, GABA and noradrenaline. Glutamatergic afferents of the basal forebrain arise primarily from cortical and amygdala areas. In addition, a prominent projection from pre-frontal cortex to BFB has recently received great attention for its important role in the modulation of executive and attentive functions (134, 64). Brainstem regions, including the pedunculopontine tegmental nucleus (PPT), may also send glutamatergic projections to the BFB. Telencephalic projections, including afferents from the amygdala, converge on BFB neurons and modulate their excitability; in particular, the substantia innominata is reciprocally connected to the basolateral amygdale (BLA) region (94, 84; reviewed in [5]). Several studies have focused on the regulation of cortical ACh efflux by GABAergic inputs to basal forebrain cholinergic neurons, presumably originating in the nucleus accumbens (AC). These studies show that basal forebrain cholinergic neurons express $GABA_A$ receptors and respond to GABAergic agonists and antagonist modifying cortical ACh release. A prominent projection is represented by noradrenergic afferents to the BFB cholinergic neurons that originate in the locus coeruleus (LC) particularly in the A5 group of the ventrolateral tegmentum. BFB cholinergic neurons receive a particularly dense noradrenergic input and the distal segments of their dendrites are repeatedly contacted by noradrenergic fibers.

Moreover, BFB nuclei receive brainstem cholinergic projections from peduncolo-pontine and laterodorsal tegmental (PPT/LDT) cholinergic nuclei (157). PPT/LDT neurons appear to activate BFB nuclei through glutamate (143), which co-localizes with choline acetyl transferase (ChAT) in these cells (102).

Thus, BFB neurons can be primarily activated by connections from prefrontal cortex (top-down) and by an ascending reticular system mainly via noradrenergic projections (bottom-up).

2. *Development.*

Neurogenesis of the rat cholinergic neurons begins at caudal level on embryonic day 12 (E12) and is completed at the most rostral level by E17 (152). ChAT, the rate limiting enzyme leading to ACh synthesis, is already detected at early embryonic stages of development (41, 66). By using an anterograde tracer method, BFB axons projecting to the cortex are detected in the white matter under the occipital cortex at postnatal day 0 (P0). At this age the occipital cortex comprises the subplate, layer VI, an emerging layer V, an undifferentiated cell dense cortical plate, and the marginal zone. At P3, when layer IV starts to differentiate

from the cortical plate, BFB axons are present in layers VI and V, while by P4 they reach layer IV. At P6, all layers of the occipital cortex are differentiated and the BFB axons are seen throughout all layers, although the vast majority of labeled axons are still confined in the infragranular layers. During the second postnatal week the axons continue to develop till reaching a pattern of mature distribution by P11 (17). Marked changes occur by P14 when the morphological features of the BFB neurons approach an adult pattern (41, 18).

ChAT immunoreactivity in the BFB reaches an intensity comparable to that of an adult by the end of the second postnatal week (41). In adult rat somatosensory cortex, ChAT immunoreactive fibers with periodic varicosities appear to form a loosely organized network throughout all cortical layers. ChAT terminals are found in association with dendrites of pyramidal neurons and somata of non-pyramidal neurons (79). ChAT activity in the rat visual cortex cannot be detected until P8. Thereafter, the level of ChAT activity increases during the second postnatal week reaching an adult-like level; this first peak was followed by a decline and subsequently by a slow increase towards adult levels (51). In contrast with data obtained by measuring ChAT activity cortical release of ACh elicited by electrical stimulation was low during the first postnatal week increasing until the end of the first postnatal month (135). Interestingly, varicosities and synaptic junctions assume adult-like features already at P8 when cholinergic innervation is installed (118).

In adulthood, the pattern of ChAT activity in the rat visual cortex shows no statistical difference among layers; however the peaks of activity were observed in layer V, I and to a less degree of intensity in layer II-III and IV (115). Overlapping results were obtained using immunohistochemistry for ChAT (117): layer V was the highest densely innervated by ChAT immunopositive fibres while layer IV was one of the lowest in parietal and occipital cortex.

Another possible marker of cholinergic fiber distribution is represented by AChE activity. At the end of the second postnatal week, AChE activity was shown to peak in layers I, and IV and the deeper part of layer III. In the third week, a peak of activity also appears in layer V. In the adult, across the thickness of primary somatosensory and visual cortex (S1 and V1), AChE reaction product is distributed throughout all cortical layers with peaks in layer I, deep layer IV, and deep layer V (119). In particular, in V1 AChE reaction product shows the highest density in layer IV with smaller peaks in layer I and V. Thus AChE cortical distribution does not clearly matches the laminar distribution of ChAT axons and varicosities (117), possibly reflecting a cortical innervation from several sources. Lesions of either the lateral geniculate nucleus (LGN) or the BFB reveal that in the first three weeks of postnatal development, the peaks of AChE activity are due to the LGN projecting neurons, with a gradual shift towards a BFB origin between the fourth postnatal week and the adulthood (72). The latter findings suggest that, since the geniculocortical pathway develops before the cholinergic projections, the peaks of AChE activity could reflect a role of the thalamic input in the formation of cholinergic synapses.

In summary, the results on cortical areas suggest that: I) BFB cholinergic neurons complete their development by the third postnatal week, and this time course is paralleled by ACh release and ChAT immunoreactivity; II) the BFB cholinergic terminals densely distribute in layers I, V and to a lesser degree in layer IV with distinct differences between the different cortical areas; III) AChE distribution throughout cortical layers does not closely match the distribution of cholinergic terminals during early stage of development.

3. *Release of Acetylcholine*.

The cortical release of ACh is almost entirely due to the activity of BFB cholinergic cells. Evoked activity (24, 21, 99) in the BFB region induces an increase of cortical cholinergic release respect to the basal rate in motor, sensory and visual cortices. Phasic and tonic release of ACh have been described in relation with phasic and tonic firing of BFB cholinergic neurons. For example, BFB cholinergic neurons receive noradrenergic projections from LC being predominantly depolarized via α_1 receptors upon noradrenaline release. Noradrenaline, then, drives cholinergic cells into a tonic mode of firing increasing their rate of repetitive spike discharge (55, 110).

The use of microdialysis techniques to measure the levels of ACh release in living animals allowed relating different behavioral and functional states of the brain with the variation of local ACh concentrations. Experimental evidence has shown that brain ACh levels can vary from few percentage points up to 800% over basal ACh release (reviewed by [137]). In absolute value, basal endogenous ACh is shown to vary in the range of concentration of hundred picomolar to nanomolar (basal ACh; [184]). Cortical ACh increase is associated with spontaneous and acquired behaviors such as exploration of a new environment (160, 63), locomotor activity (33, 23), visual attention and arousal (2, 133), chronic stress (122), sensory stimulation (50, 3), working memory and spatial learning (76,48), operant behavior (129), visuo-spatial attentional task (33) and contextual fear conditioning (125). Variations in ACh levels in the cortex as well as in the hippocampus are also associated with the wake-sleep cycle. Indeed, an increase of cholinergic release is observed during active waking as compared to slow waves sleep when the levels of ACh decrease to less than one third to rise again during the REM sleep (83, 86). Beyond the association of ACh changes with behavioral states it has been shown that patterned visual stimulation is able to elicit significant increases in acetylcholine release in the visual cortex of anaesthetized animals (101). These authors showed that the degree of cholinergic system activation is strictly related to the level of visual activity. Thus, activation of BFB cholinergic system by electric stimulation or behavioral tests may modulate the release of ACh in cholinoceptive areas respect to the basal rate.

The variation of ACh endogenous level together with the type (tonic *versus* phasic) and the cellular organization (synaptic *versus* extrasynaptic) of release concur to define the cholinergic flexibility that is necessary to accomplish for the numerous actions exerted by ACh in different cortical areas.

CHOLINERGIC RECEPTORS

The cholinergic receptors can be divided into two families: the ionotropic or nicotinic receptors (nAChRs) and the metabotropic or muscarinic receptors (mAChRs). The neuronal nicotinic receptors (nAChRs) comprises 12 subunit genes with a common ancestor, including α2 through α10 and β2 through β4. These receptors appear as pentameric ligand-gated ion channel with low selectivity for cations and able to gate high relative amounts of calcium (56). The majority of neuronal nAChRs fall into two main classes: 1) the homomeric or heteromeric α-bungarotoxin (αBgtx) sensitive receptors made up of α7, α9, α10 or

α9/α10subunits, 2) αBgtx insensitive heteromeric receptors made up of α2-α6 and β2-β4 subunits in different combinations. The α4β2 subtype was the first neuronal nicotinic receptor to be biochemically characterized and the most widely distributed in mammalian brain (176, 167). Nicotinic receptors are permeable to monovolent Na^+ and K^+ ions and to divalent Ca^{++}; permeability and ion selectivity changes as a function of subunits composition (131, 26, 39). Nicotinic receptors modulates the release of various neurotransmitters including ACh, glutamate, dopamine, noradrenaline and GABA acting at pre-synaptic sites (177). Nicotinic receptors are also capable of modulating the excitability of neurons acting at post-synaptic sites particularly in cortical interneurons (178). α4β2 nAChRs account for > 90% of the high-affinity nicotinic receptors in the brain and bind epibatidine while homomeric α7 receptors are the second most represented subtype in different regions of the brain and bind alpha-bungarotoxin, (175). Given the focus of the present review, we will not discuss in details the expression and physiological impact of all nicotinic receptor subunits in different brain areas (for recent review see [65]). A brief overview, however, is necessary to give some insights on the principal nicotinic subunits and receptors present in the visual system with particular emphasis on visual cortex areas. Visual system development and functionality requires the activity of nicotinic subunits. In particular, the β2 subunit is required in the formation of eye-specific layers at thalamic level depending on retinal waves of spontaneous activity that rely on its activation (144, 25, 67). Indeed β2 KO mice show altered retino-fugal projections that do not segregate into eye-specific areas, both in the LGN and in the superior colliculus. The idea has been raised that β2 (possibly making part of a nicotinic receptor with a (α4)3(β2)2 stoichiometry) would have a role in the nerve cell function essential for the correct wiring of the visual system during early development even before the photoreceptors are present (for a review see [49]). At the visual cortex level it has been observed that αBgtx insensitive heteromeric receptors that bind epibatidine are involved in the regulation of visual cortex responses (132). Similar data have been reported in other sensory cortices such as auditory and somatosensory cortex (136). A second widely represented nicotinic receptor in the visual system contains α7subunits (possibly homomeric). The α7receptor exhibits an extraordinary permeability to calcium ions and is particularly enriched in the cortex (for a review see [65]). Both α4and α7 subunits are distributed across all layers in the visual cortex of rat as demonstrated by antibody labeling (8). It is largely accepted that nicotinic receptors regulate thalamo-cortical synaptic transmission acting at pre-synaptic site on glutamatergic synapses. Nicotinic receptors are also expressed at post-synaptic sites as observed in somatosensory cortex (108) contributing to excitation of pyramidal and GABAergic interneurons.

The muscarinic receptor family of ACh receptors comprises five different genes (m1-m5), and is pharmacologically defined as M1-M5 subtypes, see [22]). The M_1-M_4 receptors are the most abundant mAChRs in the cortex and hippocampus (for a review see [174]). These receptors can be grouped according to the type of G proteins that they activate. Indeed, while M_2 and M_4 mAChRs are coupled to the pertussis toxin-sensitive G_i and G_o proteins, leading to the inhibition of adenylyl cyclase, the M_1 and M_3 mAChRs preferentially interact with the pertussis toxin-insensitive $G_{q/11}$ and G_{13} proteins, leading to the activation of phospholipases C and D (6, 22; for a review see [173]). The affinity of ACh is higher for M_2 and M_4 than for the M_1 or M_3 receptors (103 130). In the neocortex, the relative abundance

of mAChRs subclasses is $M_1 > > M_2 > M_4 > M_3$ (106, 105, 22). In addition the highest levels for M_1 are detected in layers II/III, and VI, where virtually all pyramidal neurons are stained. On the other hand the M_2 labeling is denser in layers IVA, IVC and at the border of layers V/VI with its immunoreactivity concentrated in spines and small dendrites of mostly interneurons (106, 123, 77, 161). The M_4 immunoreactivity, is low if compared to that of the M_1 or M_2 receptor subtypes, with the highest staining in neuropil of supragranular layers, layer V, and patches in layer IV (106, 77, 161). Equivalent results were obtained by using quantitative receptor autoradiography in the rat visual cortex (150). The laminar distribution of the different receptor subtypes in the rat brain correlates well with the cellular localization of their respective mRNAs (172).

Besides exhibiting multiple post-synaptic localizations mAChRs can also be found at the pre-synaptic sites. Pre-synaptic receptors have been described on cholinergic fibres (i.e. autoreceptors) and serve to inhibit the release of ACh. Pre-synaptic cholinergic receptors are also reported for noradrenergic, dopaminergic and glutamatergic fibres. Pre-synaptic localization of M_1-M_4 subtypes have been reported in monkey neocortex with M_2 being prominent in axons *versus* dendrites of the primate occipital cortex (42). In agreement with this observation, the selective deletion of M_2 in knock-out mice increases ACh release by reducing autoreceptor function in cerebral cortex and hippocampus (180).

There is a great body of evidence supporting that in the cortical areas, both excitatory pyramidal neurons and inhibitory interneurons express mAChRs and are modulated by ACh (159, 114, 113, 12, 73, 171, 46). Using electron microscopy Disney *et al*. (42) showed that excitatory neurons in the visual cortex of monkeys express mainly M_1 in dendrites while the soma of GABAergic neurons is the preferred subcellular site for M_2. Furthermore, in the rat somatosensory cortex muscarine affects different subclasses of layer V inhibitory neurons (178). Interestingly, there are inter-areal differences in mAChR cell expression also within regions subserving the same sensory modality. Indeed, while mAChRs are equally expressed in GABAergic interneurons across primary (V1) and secondary visual cortices their expression in glutamatergic cells varies being higher in the secondary visual cortex (42).

Interesting insights came from the autoradiographic study on the ontogenetic profile of muscarinic receptors in the rat brain. The binding sites for the total population of muscarinic receptors increase steeply between E20 and P21, while a slower increment is detected thereafter. At E20, the relative amount of M_1 binding sites in the neocortex is on average 11% of that in adults. The supragranular layers of the occipital cortex increase the number of binding sites from E20 to P35, and partially decrease thereafter. The other cortical layers stop the increment of their binding sites by P21 and decrease slightly thereafter. In the occipital cortex, the putative M_2 binding sites are still very low at P7; from P7 to P60 the density of binding sites increases steadily in all layers (7). A different temporal development of muscarinic receptor subtypes was described in mouse forebrain by using subtype specific antibodies. In this case, while M_2, as well as M_1, immunoreactivity reaches a staining pattern characteristic of the adult by P14, the intensity of the cortical immunoreactivity for M_2 continues to increase until P30 (77). Despite these discrepancies, if we consider that, the M_2 receptor is assumed to be mainly an autoreceptor at cholinergic presynaptic terminals (105), the difference in the pace of temporal maturation between M_1 and M_2 receptors subtypes could be particularly meaningful.

Altogether the reported results indicate that the different mAChRs subtypes develop precise ontogenetic profiles resulting in distinct distribution patterns throughout the different cortical layers. Additionally, results obtained using electron microscopy suggest that different mAChRs are expressed in different subcellular districts (dendrites, cell bodies and axons) of single cortical neurons with inter-areal differences in cell expression at the level of primary and secondary visual cortices.

FUNCTION OF THE CHOLINERGIC SYSTEM

The activity of the cholinergic system affects several aspects of neuronal function spreading from learning and memory to arousal, attention, plasticity of sensory maps and modulation of neuronal electrophysiological properties (21, 158, 104, 47, 154 146, 33, 29, 109). In particular damage of the cholinergic BFB can result in global cognitive impairment. For instance, aneurysms of the anterior communicating artery that injure the basal forebrain are associated with amnesia and impairment of executive function in humans (34, 40, 1). Moreover, pathological conditions that determine cognitive deficits such Alzheimer's disease are characterized by alterations in the BFB and the severity of the cognitive deficits are related to the extent of cholinergic neurons' impairment in this brain area (138, 13). In addition, experimental approaches designed to interfere with cholinergic transmission such as blocking muscarinic receptors with specific antagonist (31, 156, 4), lesions of cholinergic afferent fibres (38) or selective lesion of the BFB cholinergic neurons with the 192 IgG-saporin immunotoxin, have confirmed the importance of cholinergic transmission in memory, attention (104, 116, 169) and cortical synaptic plasticity (98).

The investigations on the physiological action of ACh in the CNS support the idea that the cholinergic system influences neuronal functions by exerting a modulatory action at three different levels: a) neural excitability b) synaptic transmission c) neuronal plasticity. The following part of this review will be focused on ACh action when mediated by muscarinic receptors.

1. *Cholinergic modulation of neuronal excitability via muscarinic receptors.*

ACh, activating mAChRs, acts as a potent regulator of neuronal activity in many classes of mammalian neurons. At the neuronal level, ACh modifies post-synaptic conductance resulting in a modulation of intrinsic excitability. In particular, application of ACh on hippocampal and cortical neurons determines membrane depolarization, an increase in membrane resistance and an increase in the firing rate of the cells (95, 112). For example, muscarinic activation in neocortical pyramidal cells through a reduction in a slow Ca(2 +)-activated K+ current I_{AHP}, and/or a voltage-dependent K+ current, I_M, results in a decrease in spike frequency adaptation and increased responsiveness to depolarizing inputs (111). All these excitatory effects are mediated through mAChRs and are due to the reduction of at least three types of potassium conductances:

1) the low-threshold slowly-activating, and non-inactivating KCNQ/M-current potassium channels (15, 170) that is a voltage-dependent outward potassium current activated by small depolarization close to the firing threshold; this current promotes membrane hyperpolarization following a spike episode (96);

2) M_1 activation reduces constitutively active inwardly rectifying K(+)(Kir2) channel currents in prefrontal cortex (PFC) pyramidal neurons. Reduction of Kir2 channel currents by M_1 receptor stimulation significantly increases the temporal summation of excitatory synaptic potentials (EPSPs) evoked by repetitive stimulation of layer I. This action was complemented by $M_{2/4}$ receptor mediated presynaptic inhibition of the same terminals. As a consequence of this dual modulation, the responses to a single, isolated afferent volley was reduced, but the response to a high-frequency afferent burst was potentiated (20);

3) mAChRs in rat cortex regulate different calcium and voltage-sensitive nonselective cation currents. These currents could represent an important mechanism through which ACh can regulate neuronal excitability in prefrontal cortex (69).

What would be the physiological impact of these two different calcium-activated non selective cation currents in neurons? Activation of IfADP (fast decay inward after current) induces a fast transient depolarization probably involved in the initial phasic firing pattern of layer V pyramidal neurons of prefrontal cortex. In contrast, activation of IsADP (slower inward after current) leads to a long-lasting sADP that can induce sustained spiking activity. Under mAChR activation these currents may act synergistically to increase neuronal excitability in response to afferent stimuli (70, 52, 93).

2. *Muscarinic modulation of synaptic transmission.*

ACh has proven to influence synaptic transmission of excitatory and inhibitory cortical neurons. This topic has been widely treated by several research groups. *In vivo* experiments conducted in the primary visual cortex tested the effects of iontophoretic application of ACh on responses elicited by visual or electrical stimulation of the LGN. It was found that the response was facilitated in 74% of the cells while it was depressed in 16%, in both cases through mAChR activation (147; see also [155]). Also, in the primary somato-sensory cortex, iontophoretic application of ACh mainly enhanced the response of single cortical neurons to whisker stimulation (43). Response enhancement was observed both in supra- and infra-granular layers, whereas response suppression was commonly observed in layer IV. Studies conducted in brain slices or in cultured cells showed much more heterogeneous and not univocal results. For instance, Cox *et al.* (30) using single cell recordings from in vitro auditory cortex observed an increase of post-synaptic response elicited in neocortical neurons by puff application of glutamate in the presence of ACh; the authors showed that this enhancement was mediated by mAChRs. A similar result was obtained by Calabresi *et al.* (17) in the striatum showing selective NMDA enhancement after muscarine application. In contrast, Vidal and Changeux (166) reported that iontophoretic application of muscarinic agonists (muscarine and acetyl-α-methylcholine) in prefrontal cortex slices, decreased EPSPs amplitude through a pre-synaptic action. Kimura and Baughman (90), using monosynaptically connected cortical cells from cultured neurons, investigated the modulatory action of ACh on both excitatory (EPSPs) and inhibitory (IPSPs) post-synaptic potentials. Their results showed an ACh dose-dependent suppression of transmission in both types of synapses that was mediated by mAChRs. The suppression of EPSPs was obtained with low concentrations of ACh through the activations of M_4 mAChR while the suppression of IPSPs was mediated by M_1 mAChR; in both cases, the action of ACh was pre-synaptic. These data obtained in cell cultures can be coupled with observations made by several groups in different cortical areas, which underline the importance of ACh con-

centration, the type of cholinergic agonist utilized and the source of connections activating cholinoceptive areas in determining the sign of cholinergic action on synaptic transmission (read facilitation *versus* inhibition). For example, Gil and colleagues (62) tested the effects of cholinergic agonists on synaptic transmission elicited by the electrical stimulation of two separate pathways: the intracortical and thalamo-cortical pathway in somatosensory cortex slices. Interestingly, they found a selective facilitation of EPSPs of thalamo-cortical synapses by nicotine while both pathways were depressed by bath application of muscarine. Remarkably, a low concentration of ACh enhanced selectively thalamo-cortical synapses similarly to nicotine. An input-dependent specificity was also reported in entorhinal cortex by Hasselmo and Bower (73). In particular, bath application of the cholinergic agonist carbachol strongly reduced the amplitude of field potentials and single cell responses in layer I neurons elicited by stimulation of intrinsic fibres. In contrast, the responses elicited by stimulation of extracortical afferent fibres were almost unchanged by carbachol. Depression of intracortical synaptic transmission in entorhinal cortex was also observed in layer II/III and layer V after bath application of carbachol (179, 27). Similar effects were induced by bath application of muscarine or ACh in the presence of the AChE inhibitor in somatosensory cortex slices (74). Recent data on entorhinal cortex using either an *in vivo* or an *in vitro* approach showed that cholinergic activation reduced the excitatory synaptic strength of inputs from pyriform cortex (71). Altogether the reported results permitted to raise the idea that intracortical connectivity, both at the level of GABAergic and glutamatergic synapses, are suppressed by muscarinic receptors, in contrast with the facilitatory action of ACh on thalamo-cortical synapses via pre-synaptic nicotinic receptors (89). However, recent results by our group (97, 98) indicated a more complex scenario where different concentrations of ACh may facilitate or inhibit excitatory synaptic transmission in the primary visual cortex by acting on different mAChRs subunits. In particular, a low concentration of exogenously applied ACh induced facilitation of synaptic transmission by activating M_4 and M_2 receptors while high ACh concentrations inhibited synaptic transmission acting on multiple mAChRs. Interestingly, the dose of ACh inducing facilitation or inhibition changes as a function of the stimulated intracortical pathway (source) and the local expression of cholinesterases (ChEs) [particularly the acetylcholinesterase (AChE), the enzyme determining the breakdown of acetylcholine and the termination of cholinergic action]. Indeed, inhibition of ChEs or the use of cholinergic agonists, which are insensitive to ChE action such as muscarine and carbachol induce a predominant inhibitory effect on synaptic transmission. We raised the idea that the degree of tonic ACh release in cortical areas should modulate the flow of information by differently influencing the responses to sensory stimuli in layers primarily responding to extracortical inputs (read layer IV) and in layers involved in the response refinement (layer II-III). Additionally, local low/high ACh levels possibly acting through the activation of different mAChRs sub-types, and the type of activated cortical connectivity would determine the sign of cholinergic modulation (facilitation *versus* inhibition).

Thus, in a more general model ACh tonic action does not simply result in facilitation or depression of synaptic transmission but rather regulates the balance between facilitation and inhibition of afferent (read thalamic) and intrinsic cortical inputs depending on local concentration of ACh, the subtypes of activated mAChRs and the local expression of ChEs.

Also the activation of nicotinic receptors is capable of modulating cortical responses mainly by enhancing glutamatergic transmission of thalamic fibers as shown in the somatosensory and prefrontal cortex (126, 100). Thus, the mechanism is similar to that displayed by muscarinic activation obtained by low ACh. However, the difference is that nicotinic responses are fast, short-lasting (< 100 msec) and rapidly desensitizing, while muscarinic responses are slow, long lasting (> 100 msec) and more resistant to desensitization. These characteristics place mAChRs in a pivotal position to integrate or suppress inputs from different sources (intrinsic versus extrinsic) in different behavioral states and then influencing visual cortical function and/or high cognitive functions. In agreement with this idea, in different brain functional studies Furey and colleagues (53, 58, 59, 60) showed that cholinergic enhancement induced by inhibition of AChE increased the responses in visual cortical areas during working memory tests in young and older healthy adults.

What is the holistic reason why ACh modulates visual responses and what would be its influence on perception, attention and/or memory? One possibility is that ACh would participate directly to the discrimination of the visual stimulus by increasing the selectivity of cortical visual neurons depending on the characteristics of sensory stimuli (for example, ACh increases the signal-to-noise ratio and the selectivity for stimulus orientation in the visual cortex; [155, 148, 183]). Following this hypothesis ACh may contribute to sculpt the visual stimuli respect to the background and in this way facilitating attentive and learning process.

A corollary hypothesis is that ACh would increase the attention for novel stimuli versus attended stimuli by modulating the encoding versus retrieval processes in visual cortical areas. In this context, a cholinergic enhancement should affect the encoding or the retrieval process, depending on how strong and, possibly, how long the activation of local cholinergic projections would be capable of modulating glutamatergic and/or GABAergic transmission in different cortical circuitries. Facilitation of extrinsic input coupled to suppression of intrinsic inputs by ACh in visual cortex as well as in other cortical areas such as the prefrontal, perirhinal and entorhinal cortex would enhance encoding of new visual information. This possibility implicitly assumes that modulation of sensory perception by ACh in sensory cortical areas represents the first step in the process of redistributing neural activity within visual cortex and other cortical areas with the aim of enhancing attention, learning and memory.

3. *Cholinergic system and synaptic plasticity.*

Different approaches have been used to show the involvement of the cholinergic system on neuronal plasticity in several brain regions. In the neocortex, homogeneous results were reported in assigning a relevant role to cholinergic innervations in modulating plastic phenomena. Depletion of cholinergic afferents to the somatosensory cortex of cats prevented the expansion of topographic maps that normally occurs after removal of one digit (85). Moreover, selective damage of the cholinergic cells of the BFB induced by 192 IgG-saporin leads to reduced neuronal activity-dependent plasticity (9, 182) and retards the development of the barrel cortex (181). Similarly, BFB cholinergic neurons modulate the reorganization of the sensory map in auditory cortex (88).

The primary visual cortex represents the most studied area for investigating mechanisms underlying neuronal activity-dependent synaptic plasticity. Manipulation of binocular

vision during a restricted time-window of early postnatal development (critical period), causes a dramatic change in visual cortex connectivity (80, 81). These pioneer studies conducted in kittens demonstrated that closing one of the eyelids for several days or weeks (monocular deprivation, MD) during the critical period shifts the ocular dominance distribution of neurons in visual cortex towards the undeprived eye. In other words, most of the neurons are driven by the stimulation of the open eye. This is particularly evident in animals that present a clear anatomical organization in ocular dominance columns such as monkeys, cats and ferrets. MD has maximal effects when performed during the critical period, which corresponds to first postnatal period but differs in length and starting point according to the mammalian species. The degree of irreversibility of MD effects varies in different species being maximal in monkeys, cats, ferrets and rats and low in mice. Sensory experience is a strong determinant for the duration of critical periods and the lack of visual experience (dark rearing) prolongs critical periods for monocular deprivation.

The combined destruction of the cortical noradrenergic and cholinergic innervations reduces the shift in ocular dominance induced by monocular deprivation during the critical period, although the alternate lesion of either system is ineffective (11). However, pharmacological blockade of cholinergic transmission by muscarinic antagonists infused into the visual cortex is by itself sufficient to suppress ocular dominance changes (68).

In order to study the cellular and biochemical mechanisms underlying brain plasticity several investigators addressed their efforts to settle experimental protocols inducing stable, reliable and consistent neuronal changes both *in vivo* and *in vitro*. The efficacy of synaptic transmission can be regulated over a wide range of temporal scales, ranging from milliseconds, to minutes and hours (short-term plasticity, long-term plasticity). Concerning long lasting modifications, two forms of synaptic plasticity can be experimentally induced: long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD can be considered part of experience-dependent synaptic plasticity that endows the brain with an ongoing ability to accommodate to a dynamically changing environment.

The expression of long term synaptic plasticity (LTP and LTD) has been extensively studied in the rat visual cortex showing that the critical period for the induction of LTP evoked by stimulation of thalamo-cortical connections almost overlaps the duration of the critical period for ocular dominance (91). This feature is much less evident in the mouse visual cortex. In addition to the thalamo-cortical connections LTP and LTD can be elicited by stimulation of intrinsic connections both during postnatal development and in adulthood. The different forms of LTP and LTD expressed in different cortical layers and elicited by the stimulation of different cortical pathways are only in part NMDA-dependent (142, 19).

Both, LTP and LTD in the visual cortex appear to be modulated by the cholinergic system. Brocher *et al.* (14) showed that LTP in layer II/III cells was facilitated by concomitant application of muscarinic and noradrenergic agonists. However, no effects were observed when each of them was administrated individually. On the other hand, Pesavento *et al.* (140) showed that a simple application of ACh in slices containing the visual cortex was sufficient to induce LTP through stimulation of mAChRs after the end of the critical period. Successively, Pesavento *et al.* (139) and Origlia *et al.* (127) using a transgenic mouse that produces antibodies against NGF and displays reduced cortical cholinergic innervation,

found an impaired LTP in visual cortex slices. Exogenous application of ACh, however, rescued LTP suggesting an essential role of this neurotransmitter in cortical synaptic plasticity. In agreement with these results Kuczewski *et al*. (97, 98) showed that the immunolesion of BFB cholinergic neurons with IgG-192 saporin was able to impair LTP in visual cortex. A biphasic action of the cholinergic system on cortical synaptic plasticity was suggested by Kirkwood *et al*. (92) who reported that, in visual cortex, also LTD is favored by cholinergic agonists such as carbachol. Origlia *et al*. (128) showed that NMDA-dependent LTP and LTD rely on the activation of different mAChRs in the primary visual cortex. Indeed, using single and double muscarinic receptor knock-out mice, they demonstrated that a normal LTP was expressed when M_2 and M_4 can be co-activated while LTD relays more on M_1 and M_3 receptor in agreement with previous results obtained by Choi *et al*. (28).

Altogether these results in visual cortex slices suggest that the direction of synaptic plasticity depends on the combined activity of different mAChRs (see Figure 1 for a drawing of mAChRs and their intracellular pathways of signal transduction involved in NMDAr-dependent forms of long term synaptic plasticity). An intriguing possibility is that ACh, by acting on different mAChR subtypes, would regulate the Bienenstock-Cooper-Munro (BMC) threshold for synaptic modification. According to the BMC model, a given synaptic stimulus may produce either LTP or LTD depending on whether or not it is able to overcome a certain modification threshold (θm; reviewed by [10]).

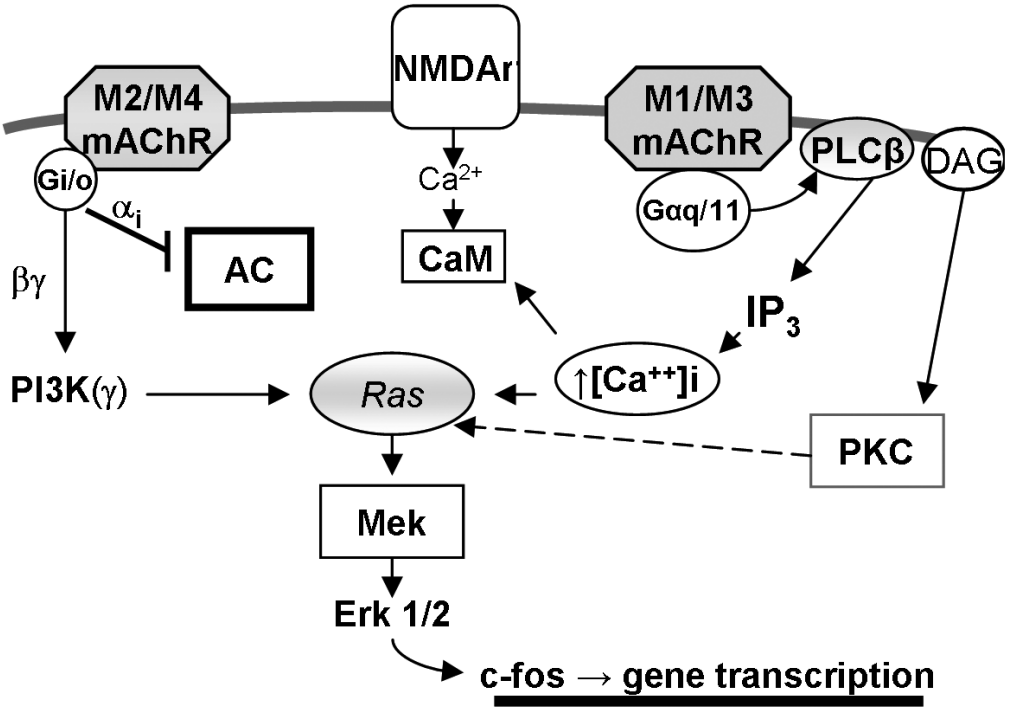

Fig. 1. - Drawing of mAChRs and their intracellular pathways of signal transduction involved in NMDAr-dependent forms of long term synaptic plasticity.

These results suggest that the cholinergic system through different mAChRs expressed in visual cortex would be able to modulate different forms of experience-dependent synaptic plasticity that are primarily driven by glutamate and NMDAr. The reported results indicate a clear relationship between ACh modulation of visual cortex plasticity during the critical period and the cholinergic influence on LTP and/or LTD.

Recent work by Tsanov and Manahan-Vaughan (162) showed that LTP and LTD in the visual cortex of freely moving adult rats, evoked by stimulation of LGN are influenced by changes in luminance levels, as it occurs during diurnal cycle. In particular, acute 12 hour light exposure leads to synaptic potentiation while acute dark rearing enhances synaptic depression. In addition, short period of monocular deprivation was sufficient to induce LTP following the stimulation of undeprived eye in adult mice (149). These data suggest that also in the adulthood the visual cortex is in a dynamic state driven by visual experience. In agreement with this idea, it is known that practicing certain visual tasks (perceptual learning) in adulthood results in high visual performance suggesting plasticity of neuronal circuitries at the cortical level (87, 57). Remarkably, perceptual training using basic visual stimuli features was able to improve visual functions in adult amblyopic patients that suffered from binocular abnormalities during the critical period (141). However, it remains to be elucidated the role of the cholinergic system and different cholinergic receptors in adult visual cortex plasticity.

CONCLUSIONS

Changes in the activity of basal forebrain cholinergic nuclei coupled with activation of different cholinergic receptors appear to be responsible for the fine modulation of cortical responsiveness to visual inputs. In particular, acetylcholine local level acting through specific muscarinic receptors subtypes is able to modulate the cortical flow of visual information. This mechanism may play a key role in switching the cortex through different cognitive states associated with high or low activation of the cholinergic system. Moreover, the direction of long term synaptic plasticity (LTP/LTD) involved in the formation and/or maintenance of cortical visual maps depends on the combined activity of different muscarinic receptors. Thus, using the visual system as a model we integrated information on pattern of cholinergic projections, including their development and maturation, distribution of muscarinic receptors and cholinesterases, local release of acetylcholine to define the cholinergic signature and the functional role of acetylcholine on neuronal plasticity and cognitive functions.

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