Muscarinic Receptors in Brain Stem and Mesopontine Cholinergic Arousal Functions

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Abstract All five muscarinic receptor subtypes and mRNAs are found widely in the brain stem, with M_2 muscarinic receptors most concentrated in the hindbrain. Three cholinergic cell groups, Ch5: pedunculopontine (PPT); Ch6: laterodorsal tegmental (LDT); Ch8: parabigeminal (PBG), are found in the tegmentum. Ch5,6 neurons are activated by arousing and reward-activating stimuli, and inhibited via M_2-like autoreceptors. Ch5,6 ascending projections activate many forebrain regions, including thalamus, basal forebrain, and orexin/hypocretin neurons (via M_3 receptors) for waking arousal and attention. Ch5,6 activation of dopamine neurons of the ventral tegmental area and substantia nigra (via M_5 receptors) increases reward-seeking and energizes motor functions. M_5 receptors on dopamine neurons facilitate brain-stimulation reward, opiate rewards and locomotion, and male ultrasonic vocalizations during mating in rodents. Ch5 cholinergic activation of superior colliculus intermediate layers facilitates fast saccades and approach turns, accompanied by nicotinic and muscarinic inhibition of the startle reflex in pons. Ch8 PBG neurons project to the outer layers of the superior colliculus only, where M_2 receptors are associated with retinotectal terminals. Ch5,6 descending projections to dorsal pontine reticular formation contribute to M_2-dependent REM sleep.

Keywords Colliculus • Dopamine • Nicotinic • Opiate • Orexin/hypocretin • Parabigeminal • Pedunculopontine • Sleep • Startle • Thalamus

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1 Brain Stem Cholinergic Cell Groups: Ch5–8 Neurons and Their Projections

Eight cholinergic cell groups were defined by Mesulam et al. (1983) using choline acetyltransferase (ChAT) labeling in rat brain. Three of these (Ch5, 6, 8) are found in the brain stem. The largest is the pedunculopontine tegmental nucleus (PPT, Ch5) which extends from the caudal end of the substantia nigra dorsocaudally into the pons (Fig. 1). The name PPT (sometimes called parabrachial n. in cats and monkeys) is due to the partial overlap of these neurons with the parallel ascending fibers of the superior cerebellar peduncle. The medial border of the elongated PPT in pons is co-extensive with the lateral border of ovoid laterodorsal tegmental nucleus (LDT, Ch6). Ch5,6 neurons together are often called "mesopontine," or sometimes "pontomesencephalic," cholinergic neurons.

The total number of mesopontine Ch5,6 neurons in the human brain was estimated at 19,400 using immunostaining for ChAT (German et al. 1999) and 18,600 neurons using NADPH diaphorase (Garcia-Rill et al. 1995) with the large majority of cells in

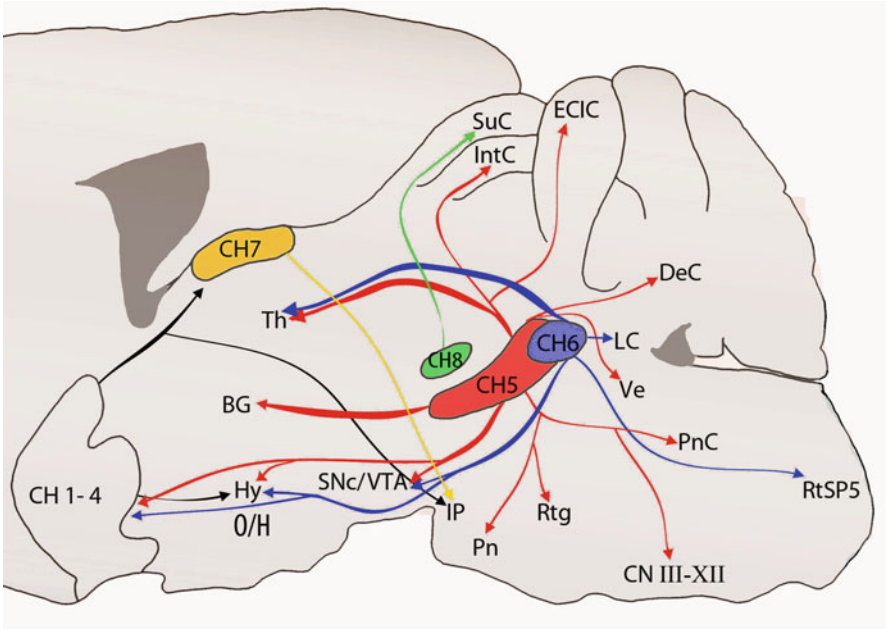

Fig. 1 Cholinergic cell groups (Ch1–8) and their brain stem projections collapsed onto a schematic parasagittal mouse brain section. *Th* thalamus, *BG* basal ganglia, *Hy* hypothalamus, *O/H* orexin/hypocretin neurons, *SuC* superficial layers of superior colliculus, *IntC* intermediate layers of superior colliculus, *ECIC* external cortex of inferior colliculus, *IP* interpeduncular nucleus, *Pn* pontine nuclei, *Rtg* rostral tegmental nucleus, *DeC* deep cerebellar nuclei, *LC* locus coeruleus, *Ve* vestibular nuclei, *PnC* nucleus reticularis pontis caudalis, *CN* cranial nerves, *RtSP5* spinal nucleus of the 5th nerve

Ch5. A smaller midbrain cell group that projects to the outer layers of the superior colliculus is the parabigeminal nucleus (Ch8), on the lateral edge of the rostral tegmentum, lateral to the rostral PPT. All cholinergic cell groups are found in nuclei that include non-cholinergic glutamate and GABA neurons as well.

Ch7 neurons of the medial habenula (dorsal to thalamus) project to the interpeduncular nucleus of the midbrain, just ventromedial to ventral tegmental area (VTA) dopamine neurons. Basal forebrain cholinergic neurons (Ch1–4) project only to the forebrain (especially olfactory bulb, amygdala, cerebral cortex, and hippocampus, with a small projection to the hypothalamus) and to the habenula and midbrain interpeduncular n., and so are discussed in other chapters. Cholinergic interneurons in the striatum and possibly other brain areas will not be discussed here.

Within the brain stem, many groups of cholinergic motoneurons are found (for cranial nerves III, IV, V, VI, VII, IX, X, XI, and XII). Their projections are to muscles and ganglia outside the central nervous system, and so are discussed elsewhere in connection with peripheral muscarinic receptors.

1.1 Functions and Forebrain Projections of Ch5 and Ch6 Neurons

Mesopontine Ch5 and Ch6 neurons (unlike Ch7 and Ch8 neurons) project to dozens of brain stem and subcortical nuclei with many functions (Woolf 1991; Semba and Fibiger 1992; Steininger et al. 1992). Ch5 and Ch6 neurons in many species are active in waking and/or REM sleep states associated with cortical arousal (Steriade and McCarley 2005; Kayama and Koyama 2003) and with reward-associated events (Pan and Hyland 2005; Kobayashi and Okada 2007). Ch5,6 projections activate many neurons in the thalamus, basal forebrain, hypothalamus (e.g., orexin-hypocretin neurons), and tegmentum (e.g., dopamine neurons) (Semba 1993; Yeomans et al. 2001; Sakurai et al. 2005; Yamanaka et al. 2003; Bayer et al. 2005). This "Mesopontine Cholinergic Arousal System" thereby facilitates neocortical electrical activity in waking or REM sleep, and behavioral arousal in waking states (Steriade and McCarley 2005; Yeomans et al. 1993).

Virtually all Ch5 and Ch6 neurons project to the thalamus, but each of these neurons also has axons projecting to other brain stem nuclei (Cornwall et al. 1990; Oakman et al. 1995, 1999; Woolf and Butcher 1986). A few neurons send axons that project to basal forebrain cholinergic neurons, but many more project to basal ganglia (e.g., globus pallidus, subthalamic nucleus), hypothalamus (e.g., suprachiasmatic, ventromedial hypothalamus, orexin/hypocretin neurons of the lateral hypothalamus), midbrain tegmentum (raphe n., rostromedial tegmental n., VTA and substantia nigra), tectum (pretectal nucleus, superior and inferior colliculi), cerebellum deep nuclei and cortex, or to pontine and medullary tegmentum (e.g., pontine nuclei, locus coeruleus, pontine reticular formation, vestibular nuclei, and several cranial nerve nuclei) (Semba and Fibiger 1992; Woolf and

Butcher 1986). Ch5 and Ch6 neurons project to many of the same nuclei with little topographic separation, but rostroventral PPT neurons have stronger projections to basal ganglia, including substantia nigra, subthalamic nucleus, and globus pallidus, while LDT neurons project more to medial hypothalamus and thalamus (Woolf and Butcher 1986; Mena-Segovia et al. 2008).

The functions of the M_1–M_5 muscarinic subtypes in brain stem will be reviewed here, especially in relation to the hypothesis that mesopontine cholinergic neurons act in a coordinated way to facilitate arousal, attention, motor activity, and reward seeking.

2 Localization of Muscarinic Receptors and mRNA in Brain Stem

Immunoprecipitation showed that M_1 receptor proteins are highest in whole telencephalon samples ($M_1 > M_4 > M_2 > M_3 >> M_5$), M_2 receptors are slightly higher in midbrain samples ($M_2 > M_1 > M_4 > M_3 > M_5$) while M_2 receptors are by far the highest in hindbrain and cerebellum samples (>70%) ($M_2 >> M_3 = M_1 = M_4 > M_5$) (Yasuda et al. 1993). Immunocytochemistry localized these receptors, with M_2 receptors widely distributed in brain stem, but most concentrated in the outer layers of the superior colliculus, in pontine and pretectal nuclei, and in Ch5, 6, and 8 cell groups (Levey et al. 1994). Several motoneuron groups (e.g., V and VII) show high levels of M_2 receptors along with lower levels of M_1, M_3, and M_4 receptors. These muscarinic receptor densities are associated with acetylcholinesterase (AChE) staining of these brain stem nuclei, in human (Paxinos and Huang 1995), rat (Paxinos and Watson 2007), or mouse (Franklin and Paxinos 1997).

Low levels of brainstem M_4 receptors are concentrated in the hypothalamus and in brainstem motoneurons. M_5 receptors account for only about 1% of all brain receptors so localization of M_5 receptors using immunocytochemistry was not reported (Levey 1993).

Physiological studies showed that M_1, M_3, and M_5 receptors activate Gαq/11 proteins and phospholipase C in vitro, which can depolarize neurons and stimulate peripheral secretions (Bymaster et al. 2003). M_2 and M_4 receptors, however, activate Gαi/o proteins that inhibit adenylyl cyclase, and hyperpolarize heart muscles and cholinergic neurons. It has been proposed that M_1, M_3, and M_5 are postsynaptic excitatory receptors, while M_2 and M_4 receptors are inhibitory, both pre- and postsynaptic, and as inhibitory autoreceptors on cholinergic neurons (Levey 1993; Wess et al. 2003; Bymaster et al. 2003). In vitro studies suggested that M_2 receptors bind more quickly than M_1 and M_4 receptors, with M_3 and M_5 receptors binding more slowly (Flynn et al. 1997; Ferrari-diLeo et al. 1994).

In situ hybridization locates mRNA for each of the five receptors (Weiner et al. 1990; Lein et al. 2007). This method helps show the cholinergic and non-cholinergic neurons expressing the receptors. For example, detection of M_5 mRNA in VTA

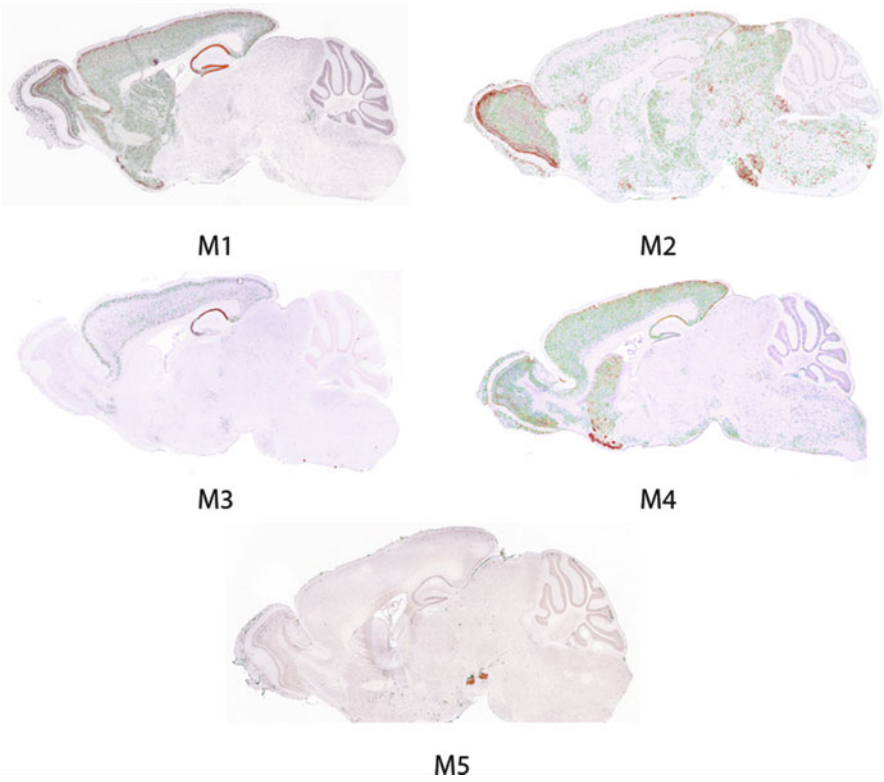

Fig. 2 Muscarinic receptor mRNA density for each of the five muscarinic receptors in mouse. Each section shows density placed on cresyl violet-stained parasagittal sections about 1 mm off the midline of sections from the Allen Mouse Brain Atlas (Lein et al. 2007). The pseudocolor density scales proceed from *green* (low) to *red* (highest) on each section of the e-book, and are set differently on each section to highlight the areas of highest density for each receptor mRNA. For *black* and *white* figures, densities are scaled from *darkest (black)* to *lightest (white)* on a *gray* scale

and substantia nigra, pars compacta, removable by 6-hydroxydopamine, led to evidence that DA neurons are excited by M_5 postsynaptic receptors (Weiner et al. 1990; Vilaro et al. 1990; Yeomans et al. 2001). Figure 2 shows parasagittal sections taken approximately 0.6 mm off the midline for each of the M_1–M_5 mRNAs and AChE mRNA. Again, M_2 mRNA expression is highest in the brain stem, followed by M_3, with M_1, M_4, and M_5 much lower. M_1 mRNA is found at low levels in hypothalamus and motoneuron cell groups (III, V, VI, VII, X, XII).

M_2 mRNA is found near the cell bodies of all Ch5–8 cell groups, with highest levels in pontine nuclei. Moderate levels are found in thalamus (especially the reticular nucleus that inhibits other thalamic nuclei) and widely in the brain stem from the outer layers of the superior colliculus to the caudal medulla. M_2, M_3, and M_5 mRNAs are found near Ch8 parabigeminal neurons, and in the lateral habenula (Vilaro et al. 1994).

M_3 mRNA is found near orexin/hypocretin neurons of the lateral hypothalamus, in several nuclei of the thalamus, and on interpeduncular and pontine n. neurons in the midbrain, as well as superior and inferior colliculus. M_4 mRNA is found near ventral brainstem motoneurons, like M_1, but rarely elsewhere. M_5 mRNA is localized to DA neurons in VTA and SNC and in the ventromedial hypothalamic nucleus.

3 Muscarinic Receptor Functions in Diencephalon and Basal Forebrain: Ascending Mesopontine Cholinergic Arousal

Muscarinic receptors on Ch5,6 neurons are strongly inhibitory, acting via M_2-like receptors and K^+ channels (Leonard and Llinas 1994; Luebke et al. 1993). Both autoreceptors and cholinergic inhibitory synapses are found, suggesting that cholinergic arousal is held in check by somatodendritic autoreceptors and by postsynaptic release of ACh (Leonard, personal communication).

In thalamus, muscarinic inputs are largely excitatory, except for inhibition of reticular n. GABA neurons that tonically inhibit other thalamic nuclei (Steriade 1993; McCormick 1989). These muscarinic inputs, therefore, facilitate thalamic systems, resulting in widespread thalamocortical activation during waking and REM sleep (Steriade and McCarley 2005). Cholinergic facilitation of cortical functions is thereby initiated via mesopontine cholinergic neurons and then is relayed via excitation of thalamus and of basal forebrain cholinergic neurons (Dringenberg and Olmstead 2003).

Muscarinic receptors in the intergeniculate leaflet (IGL) of the thalamus can shift circadian rhythm in hamsters (Cain et al. 2007). In particular, PPT cholinergic neurons that respond to arousing signals are believed to activate IGL neurons that mediate arousal-induced phase shifts by way of direct IGL projections to the suprachiasmatic nucleus (SCN).

Cholinergic inputs to the SCN can alter circadian rhythms especially at night (e.g., Liu and Gillette 1996). Basal forebrain and PPT cholinergic neurons project to SCN (Bina et al. 1993), so either pathway could provide the cholinergic influence on SCN. All five muscarinic mRNAs are expressed in SCN neurons, but M_1- and M_4-like receptors seem to be most effective in mediating carbachol-induced hyperpolarization in SCN neurons, in vitro (Yang et al. 2009). M_1-like receptors are most important in mediating the nighttime effects of carbachol in SCN on circadian rhythms (Gillette et al. 2001).

Orexin/hypocretin neurons in the lateral hypothalamic perifornical area help maintain waking arousal, and are lost in narcolepsy/cataplexy (Thannickal et al. 2001). Many of these neurons are strongly depolarized and excited by 100 μM carbachol, an effect that is blocked by atropine, or the M_3 antagonist 4-DAMP (Yamanaka et al. 2003; Bayer et al. 2005). These cholinergic inputs to orexin/hypocretin neurons could come from either Ch1–4 basal forebrain (Henny and

Jones 2006) or Ch5,6 neurons (Ford et al. 1995). Orexin/hypocretin neurons, in turn, directly and indirectly excite LDT Ch6 cholinergic neurons (Burlet et al. 2002; Takahashi et al. 2002).

4 Functions of Muscarinic Inputs to Substantia Nigra and VTA

Stimulation of PPT or LDT results in monosynaptic excitation of dopamine (DA) neurons of the substantia nigra and VTA (Lacey et al. 1990; Futami et al. 1995; Scarnati et al. 1986). These cholinergic inputs are important for the maintenance of burst firing in DA neurons (Lodge and Grace 2006; Floresco et al. 2003). Anatomical studies show many ChAT-labeled terminals in the vicinity of dopamine and non-dopamine neurons (Beninato and Spencer 1988; Bolam et al. 1991; Sesack and Grace 2010) along with eight nicotinic (alpha 3–7, beta 2–4) and four muscarinic (M_{2-5}) receptor subtypes (Klink et al. 2001). MRNA studies, however, indicate that M_5 receptors are made by only DA neurons, since all M_5 mRNA and M_5-like receptors are lost after 6-hydroxydopamine lesions of DA neurons (Weiner et al. 1990; Vilaro et al. 1990; Reever et al. 1997).

The muscarinic receptors affecting net dopamine output can be studied by recording DA efflux in the nucleus accumbens or striatum. When the PPT or LDT is electrically stimulated, DA efflux is increased in accumbens or striatum for 1–3 min, due to ionotropic nicotinic and glutamate receptors in VTA or SN (Forster and Blaha 2000). DA efflux is reduced from 2 to 8 min after stimulation due to M_2-like receptors in LDT or PPT. Then, a second wave of DA efflux occurs from 8 to 60 min in rats, or 5 to 40 min in mice. This prolonged DA output is completely blocked by muscarinic receptor blockers in the VTA, or by knockout of the M_5 muscarinic receptor in mice (Forster et al. 2002). This very slow M_5 effect is consistent with the very slow binding of M_5 receptors in cell cultures (Ferrari-diLeo et al. 1994) or in salivation (Takeuchi et al. 2002). Therefore, sustained activation of dopamine neurons results from postsynaptic M_5 excitation of DA neurons from PPT and LDT cholinergic neurons (Yeomans et al. 2001).

Muscarinic receptors on non-dopamine neurons and terminals in VTA and substantia nigra have a strong net inhibitory effect on dopamine outputs, and on locomotor activity (Steidl and Yeomans 2009). The muscarinic blocker atropine in VTA facilitated locomotor activity strongly in M_5 knockout mice, for example, but had much less effect in wild type mice. Although M_2 muscarinic receptors are found on terminals and dendrites of many VTA neuron types (Garzón and Pickel 2006), the M_4 muscarinic receptor especially inhibits ACh release from PPT/LDT terminals in the VTA/SN (Tzavara et al. 2004). That is, M_4 knockout mice show increased ACh release in VTA, but M_2 knockout mice do not. M_3 muscarinic receptors are found postsynaptically in VTA, and may provide an excitatory influence on GABA neurons (Michel et al. 2005; Miller et al. 2005). A model of VTA/SN muscarinic effects on DA neurons is shown in Fig. 3.

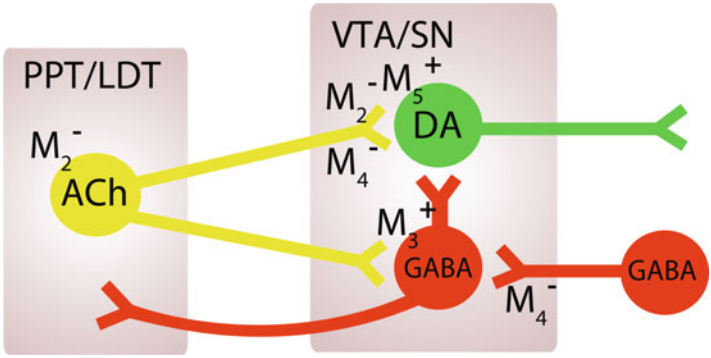

Fig. 3 Muscarinic subtypes affecting PPT/LDT cholinergic, and VTA/SN DA and GABA neurons (model based on Miller et al. 2005; Tzavara et al. 2004; Steidl and Yeomans 2009)

4.1 Reward-Related Behaviors and M_5 Muscarinic Receptors

M_5 receptors are also important for the rewarding effects of hypothalamic stimulation, of carbachol in VTA, of opiates, and of ethanol. Muscarinic blockers in VTA strongly reduce the rewarding effects of hypothalamic stimulation in rats (Kofman et al. 1990; Yeomans et al. 1985). A similar reduction in sensitivity occurs after knockdown of the M_5 muscarinic receptor in VTA by infusions of an antisense oligonucleotide (Yeomans et al. 2001). Muscarinic receptor blockers in VTA also reduced the rewarding effects of food in rats (Sharf et al. 2005; Sharf and Ranaldi 2006). In this regard, hypothalamic brain-stimulation reward, feeding and drinking are known to activate PPT cholinergic neurons and to induce release of acetylcholine into the VTA from cholinergic terminals (Pan and Hyland 2005; Rada et al. 2000).

Fifty kHz ultrasonic vocalizations (USVs) induced in male mice by female urine, or during mating, are reduced by 70–80% in M_5 knockout mice, even though mating appears normal (Wang et al. 2008). This deficit is likely due to reduced activation of dopamine neurons that facilitate USVs. M_5 receptors found in the ventromedial hypothalamic nucleus may be related to USVs, too, because microlesions of ventromedial hypothalamus also reduce male USVs, without disrupting mating (Harding and McGinnis 2005).

Carbachol in VTA is strongly rewarding in rats, either in conditioned place preference tasks (Yeomans et al. 1985) or when self-administered in VTA (Ikemoto and Wise 2002). Although carbachol acts on both nicotinic and muscarinic receptors, the rewarding effects of carbachol are blocked by muscarinic, but not nicotinic, blockers in VTA (Ikemoto and Wise 2002). The weaker rewarding effects of systemic nicotine, however, are blocked by nicotinic blockers in VTA (Corrigall et al. 1994).

4.2 Opiates and Reward

Small bilateral lesions of the caudal PPT block the rewarding effects of opiates, either in conditioned place preference or intravenous self-administration acquisition tasks (Bechara and van der Kooy 1989; Laviolette and van der Kooy 2004; Olmstead and Franklin 1993). Also, carbachol in PPT inhibits sensitivity to brain-stimulation reward or to ethanol intake, presumably by inhibiting cholinergic neurons in PPT (Yeomans et al. 1993; Mathur et al. 1997). By contrast, scopolamine in PPT increases brain-stimulation reward sensitivity and increases striatal dopamine release (Yeomans et al. 1993; Chapman et al. 1997).

Morphine (20–25 mg/kg i.p.) increases accumbal dopamine release in rats or mice (Basile et al. 2002). Ch5,6 lesions, or VTA/nigral infusions of the muscarinic blocker scopolamine, blocked the ability of morphine, but not amphetamine, to increase DA release in the accumbens or striatum (Miller et al. 2005). In M_5 knockout mice, morphine fails to increase accumbal DA release, except in the first 20 min after infusion when ionotropic receptors are used (Basile et al. 2002). Also M_5 knockout mice show less conditioned place preference (1–30 mg/kg) and less locomotion in response to morphine (3–30 mg/kg) (Basile et al. 2002; Steidl and Yeomans 2009). VTA infusions of the muscarinic blocker atropine reduced the locomotor stimulant effect of morphine similarly. Finally, naltrexone had less inhibitory effect on spontaneous locomotion or on USVs in M_5 knockout mice, suggesting that endogenous opiates also work via M_5 receptors in VTA to stimulate dopamine neurons. Therefore, both systemically applied or endogenous opiates depend on muscarinic M_5 activation in VTA/nigra to stimulate dopamine neurons or to stimulate dopamine-dependent forms of locomotion and reward-seeking (Steidl and Yeomans 2009).

A role for muscarinic receptors in PPT and VTA in ethanol intake has been proposed (Katner et al. 1997). The reduction of ethanol intake and ethanol-induced dopamine release by naltrexone (Middaugh et al. 2003) suggests that muscarinic receptors contribute especially to the opiate receptor-dependent part of ethanol drinking.

5 PPT, Basal Ganglia and Parkinson's Disease

Brains of Parkinson's patients often have severe loss of PPT neurons as well as ventrolateral nigral neurons (Pahapill and Lozano 2000; Zweig et al. 1989). Unilateral deep brain stimulation of the PPT has recently been found to relieve gait freezing and postural instability in advanced Parkinson's Disease when dopaminergic drugs are no longer effective (Plaha and Gill 2005; Pereira et al. 2008). Unlike deep brain stimulation of subthalamic nucleus, low frequency stimulation (20–25 Hz) is most effective. The mechanisms of these beneficial effects are not

yet clear, but the ascending pathways from the lateral PPT to basal ganglia are most often considered.

In addition, substantia nigra pars reticulata neurons strongly inhibit PPT cholinergic neurons via monosynaptic GABA receptors (Takakusaki et al. 1996). These connections are relevant to the control of REM sleep and atonia (Takakusaki et al. 2004) as well as ascending influences on basal ganglia. In this regard, the locomotor facilitating effects of PPT stimulation in humans, primates and rats, and the locomotor inhibiting effects of PPT inhibition, are relevant (Nandi et al. 2008; Brudzynski et al. 1988; Mathur et al. 1997). More work is needed on the muscarinic receptors needed for PPT-induced locomotion in M_1–M_5 knockout mice.

6 Descending Cholinergic Pathways in REM Sleep

A subset of Ch5 and Ch6 cholinergic neurons are active just before the onset of REM sleep, suggesting a special role of these neurons in initiating cortical arousal during dreams (Steriade and McCarley 2005; Kayama et al. 1992; Semba 1993). Because these REM-on neurons are interspersed within a larger population of Ch5 neurons that respond only during waking arousal, the critical REM-on neurons have not been identified (Datta 2002). Takakusaki et al. (2004) proposed that REM-on neurons are located in a more dorsal layer of Ch5 cells that, in turn, project to the pontine tegmental area critical for triggering REM onset. In particular, M_2-like muscarinic receptors in the dorsal pontine tegmentum behind PPT and LDT contribute to REM sleep generation in mice (Coleman et al. 2004).

7 Eye Movements, Approach Turns, and Startle Inhibition Due to Muscarinic Receptors in Colliculi and Brain Stem

PPT cholinergic neurons project to intermediate gray layers of the superior colliculus (SCi), where auditory, tactile, and visual inputs converge on premotor neurons that initiate fast saccadic eye movements (Isa and Hall 2009). SCi neurons activate saccadic eye movements and head turns toward visual targets (i.e., "approach turns") by way of crossed tectoreticulospinal axons to premotor nuclei controlling vertical and horizontal eye movements. Both nicotinic and muscarinic inputs to these SCi neurons are excitatory, thereby facilitating fast saccades.

The muscarinic facilitation of SCi neurons in vitro has been shown to involve an inward postsynaptic current working mainly via M_3-like receptors (i.e., blocked by 4-DAMP), with a small M_1 effect blocked by pirenzepine (Sooksawate and Isa 2006). In addition a small inhibitory outward current via M_2 receptors, and a presynaptic reduction in GABA inhibition, occurs.

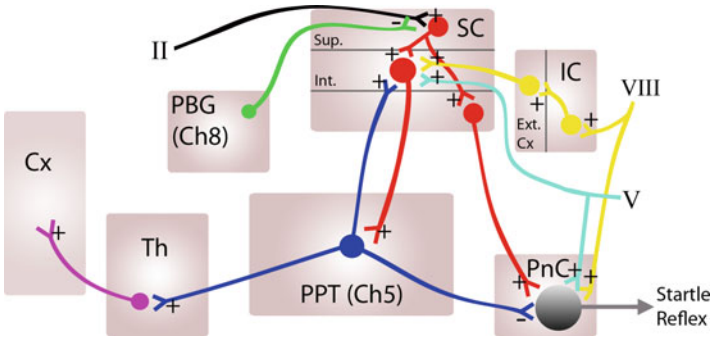

Fig. 4 Model of cholinergic influences on approach turns in superior and inferior colliculi and brain stem, including simultaneous activation of thalamus, and inhibition of startle reflex circuits in pons. Abbreviations are the same as Fig. 1

Auditory inputs to the SCi come from the external cortex of the inferior colliculus, which also receives direct projections from PPT cholinergic neurons. AChE is concentrated in layer 2 of the external cortex, but the muscarinic inputs have not been studied.

By contrast, parabigeminal Ch8 neurons project only to the outer layers of SC, where high levels of M_2 receptors and AChE are found in the outer, visual layers of the SC (see Figs. 1 and 4). ACh results in less depolarization of these superficial neurons by visual glutamate inputs. These inhibitory effects are mediated by parabigeminal inputs to superficial layer neurons (Isa and Hall 2009).

7.1 Cholinergic Inhibition of the Startle Reflex Following Prepulses

Although high-intensity stimulation of the inferior or superior colliculus activates the startle reflex, moderate-intensity stimulation inhibits startle (Fendt et al. 2001; Yeomans et al. 2006). In rats, inferior colliculus lesions block prepulse inhibition of startle by moderate-intensity acoustic prepulses (Leitner and Cohen 1985) while superior colliculus mediates a slower inhibition of startle by visual, tactile, or auditory prepulses (Fendt et al. 2001; Yeomans et al. 2006). The lowest threshold sites for startle inhibition by electrical stimulation are found in SCi associated with activation of tectoreticulospinal neurons initiating approach saccades and turns (Yeomans et al. 2006; Sahibzada et al. 1986; Tehovnik and Yeomans 1986).

Prepulse inhibition results mainly from descending cholinergic projections of the PPT to the pons. PPT lesions block prepulse inhibition of startle in rats (Koch et al. 1993; Swerdlow and Geyer 1993). PPT stimulation inhibits giant neurons in the ventrocaudal pontine reticular formation (PnC) that elicit startle (Bosch and Schmid 2008; Yeomans et al. 2001). Carbachol inhibits PnC giant neurons via both

nicotinic and muscarinic receptors (Bosch and Schmid 2006, 2008). Muscarinic receptors mediate startle inhibition 100–500 ms after prepulse delivery (Yeomans et al. 2010).

These mesopontine cholinergic inhibitory effects on startle parallel the timing of PPT-mediated facilitation of fast saccades in SCi. Accordingly, PPT cholinergic neurons simultaneously facilitate approach saccades via activation of SCi tectoreticulospinal neurons, and inhibit startle-mediated eye closure via inhibition of PnC startle neurons, allowing rapid foveation of targets. Mesopontine cholinergic neurons, therefore, appear to coordinate approach turns, whereby turning to look is accompanied by startle inhibition that prevents eye closure.

Simultaneously, mesopontine cholinergic arousal facilitates thalamocortical systems needed for attention and analysis of incoming signals (Fig. 4). This cortical activation prepares the forebrain for analysis of incoming sensory information.

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