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Medial septal/diagonal band cells express multiple functional nicotinic receptor subtypes that are correlated with firing frequency

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Abstract

The medial septum-diagonal band (MS/DB) contains primarily cholinergic and GABAergic neurons that project to the hippocampus, and are important for learning and memory. Whole-cell patch clamp methods with brain slices from p11–p20 rats were used to measure MS/DB cell responses to focal somatic application of 1 mM acetylcholine (ACh) and a series of current pulses was applied in order to assess firing frequencies and the presence of hyperpolarization-activated currents (Ih). We identified three types of cells: (1) cells with fast inward currents blocked by methyllycaconitine (MLA) with slow firing rates (3–12 Hz), accommodating action potentials, and no Ih ($n = 20$); (2) cells with currents that had both fast (MLA-sensitive) and slow components that were blocked with mecamylamine (MEC) that showed fast firing (up to 60 Hz) and slow firing (up to 3 Hz), with accommodating and non-accommodating action potentials ($n = 46$), 33% of which had Ih; and (3) cells not responsive to ACh with moderate firing rates (10–42 Hz), some with accommodating action potentials and some without ($n = 19$), of which 92% had Ih. These results are among the first to demonstrate functional nicotinic receptors in the MS/DB. The data suggest that these receptors include α7 and non-α7 subtypes and that the expression of each is correlated with firing frequency and the presence of Ih. Responses to ACh were not affected by tetrodotoxin (TTX) and $CdCl_2$ but were blocked by MLA or MLA and MEC, suggesting that these currents involve direct activation of nicotinic receptors.

Keywords: Alpha 7; Septohippocampal; Septum; Nicotinic; MSDB; Alpha 4 beta 2

Neurons in the medial septum/diagonal band of Broca (MS/DB) are primarily cholinergic and GABAergic cells that project to the hippocampus and regulate excitability of principal cells and interneurons [7,11]. The septohippocampal pathway is important for learning and memory-related behaviors, and degeneration of cholinergic MS/DB neurons can be seen in neuropathological disorders such as Alzheimer's disease [3]. Firing patterns of MS/DB neurons are linked with their neurochemical identities such that fast firing cells generating current in response to hyperpolarization (Ih) have been shown to be GABAergic and slow firing cells with no Ih cholinergic [8,9].

Relative to other brain regions such as the hippocampus [2,5,12], there has been a paucity of information regarding the presence of functional nicotinic receptors in the MS/DB. The initial reports describing single MS/DB cell nicotinic responses showed that iontophoretic application of nicotine inhibited cell firing as measured by extracellular recordings in vivo [24,25]. In the brain slice, recent work by Wu et al. [23] suggested that depolarization produced by activation of MS/DB nicotinic receptors could occur only indirectly through presynaptic mechanisms, involving action potential-dependent glutamate release. These authors argued that there

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was little evidence for MS/DB α7 nicotinic receptors based on data (1) showing methyllycaconitine (MLA) was ineffective at blocking depolarizations produced by 20-s applications of nicotine, and (2) data from other groups [22] in which α7 receptors were not detected in the septum. More recently, however, Henderson et al. [10] showed evidence for direct activation of MS/DB cholinergic receptors with focal somatic "puff" applications of acetylcholine (ACh). These authors reported that depolarizations in response to ACh were blocked with the nicotinic receptor antagonist mecamylamine (MEC) (25 μM) and partially or not blocked with tetrodotoxin (TTX), $CdCl_2$, or antagonists of other ionotropic receptors. Also, Henderson et al. [10] reported MLA-sensitive currents, suggesting the presence of MS/DB α7 nicotinic receptors. Since the available data regarding MS/DB nicotinic receptors are limited and conflicting, we used whole-cell patch clamp methods to assess MS/DB cell firing frequencies, the presence of Ih and responses to focal somatic ACh application. Evoked responses to ACh were also tested for sensitivity to MEC, MLA, TTX and $CdCl_2$.

Transverse whole brain slices from male Sprague–Dawley rats (p11–p20) were prepared as described previously [21]. During experiments, slices were perfused (2 ml/min) with normal ACSF containing (in mM) 126 NaCl, 3 KCl, 1.2 NaH_2PO_4, 1.5 $MgSO_4$, 11 D-glucose, 2.4 $CaCl_2$, 25.9 $NaHCO_3$ and 0.008 atropine sulfate saturated with 95% O_2–5% CO_2 at 30 °C. MS/DB cells were visualized with infrared differential interference contrast microscopy (IR DIC) using a Nikon E600FN microscope. Whole-cell patch clamp recordings were made with glass pipettes (3–5 MΩ) containing an internal solution of (in mM) 125 K-gluconate, 1 KCl, 0.1 $CaCl_2$, 2 $MgCl_2$, 1 EGTA, 2 MgATP, 0.3 Na_3GTP and 10 HEPES. Cells were held at −70 mV and a −10 mV/10 ms test pulse was used to determine series and input resistances. Cells with series resistances >52 MΩ or those requiring holding currents >250 pA were not included in the final analysis. Series resistance average was 20.9 ± 1.4 MΩ. Responses to somatic application of ACh were measured in voltage clamp mode and responses to current injections were measured in current clamp mode. Signal acquisition and data analyses were done as previously described [21]. Focal somatic application of ACh (1 mM) was performed with pipettes attached to a Picospritzer II (General Valve, Fairfield, NJ, USA) using 10–20 psi for 5–30 ms.

In experiments using MLA, MEC, TTX, or $CdCl_2$, baseline responses to ACh were recorded every 30 s for 2 min and the above antagonists/toxins were then introduced using a syringe pump (Kd Scientific, Holliston, MA, USA). For TTX and $CdCl_2$ experiments, responses were measured for 8 min after the beginning of bath application and in some cases this was followed by application of both MLA and MEC. For MLA experiments, responses were recorded for 2–3 min after no evoked response could be detected. For experiments using both MLA and MEC, responses were recorded until there was a stable reduction in evoked current in the presence of MLA (2.5–7.5 min) and then MEC was added to the bath and responses were recorded for 2–3 min after no evoked response could be detected.

To assess firing frequency and currents in response to hyperpolarization (Ih), a series of hyper- and depolarizing currents was applied. The membrane potential of each cell was first held at −75 mV and a series of (1 s) hyper- and depolarizing pulses (0–200 pA) were applied. The membrane was then adjusted to −60 mV and the same series of pulses were applied. Resulting voltages were ∼−150 mV for maximum hyperpolarization and ∼−20 mV for maximum depolarization. Firing frequencies for each cell were determined with the series from the −60 mV membrane potential using the same current pulse required to depolarize the cell to threshold from −75 mV [11]. Accommodation was defined as a reduction in firing rate when comparing the first 0.5 s of depolarization to the second 0.5 s and the presence of Ih was evaluated using the first hyperpolarizing pulse from −60 mV. Cells were classified as either positive or negative for Ih based on the presence of a clear depolarizing sag [8].

Three basic nicotinic response profiles were identified based on responses to focal somatic application of ACh in the presence of atropine. Type-1 cells ($n = 20$) responded to ACh with fast inward currents (time to peak = 28.4 ± 0.8 ms) (Fig. 1A). The peak current amplitudes were 138 ± 21.5 pA and these were blocked by the α7-selective antagonist MLA (50 nM, $n = 9$) (Fig. 1B and C). Type-1 cells had slow firing rates (7.0 ± 1.0 Hz) and all had accommodating action potentials (Fig. 2A). No type-1 cell showed Ih in response to hyperpolarization.

Type-2 cells ($n = 46$) responded to ACh with slow (time to peak = 235.4 ± 28.1 ms) (Fig. 1G) and a combination of both slow and fast inward currents (time to peak = 35.2 ± 4.2 ms) (Fig. 1D). These currents were completely blocked with 5 μM MEC ($n = 11$) and contained both MLA-sensitive (50 nM) and MLA-resistant components (Fig. 1E, F, H and I). Type-2 cells were divided into two groups (2A and 2B). Type-2A cells ($n = 28$) had biphasic kinetic profiles containing a well-defined fast and slow component (Fig. 1D) with peak current amplitudes of 172 ± 25.1 pA and on average had moderate or slow firing rates (10.5 ± 1.7 Hz) (Fig. 2B). In 23% of these cells, Ih was present and 54.5% showed accommodation. Cells classified as type-2B had monophasic kinetic profiles (Fig. 1G) ($n = 18$) and peak ACh-evoked current amplitudes of 78.3 ± 10.7 pA. On average, Type-2B cells had fast firing action potentials in response to depolarizing steps (27.9 ± 6.9 Hz) (Fig. 2C). In 63% of type-2B cells, Ih was present and 12.5% of these cells showed accommodation.

It is known that MLA-sensitive currents (putatively mediated by α7 receptors) have faster activation kinetics than MLA-resistant currents [19]. In type-2 cells, the presence of two distinct activation kinetic profiles could reflect differences in the ratio of MLA-sensitive and MLA-resistant nicotinic receptor subtypes. In support of this, type-2B cells had much slower time-to-peak values (235.4 ± 28.1 ms) than type-2A cells (35.2 ± 4.2 ms), and following application of 50 nM MLA, peak currents from type-2B cells were reduced

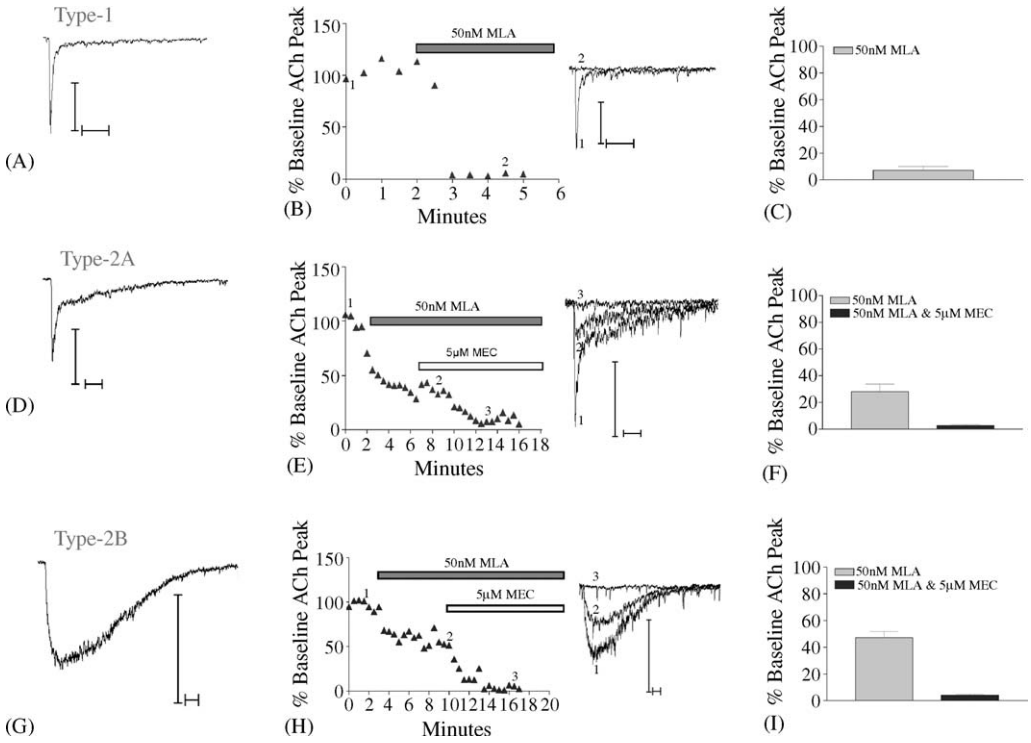

Fig. 1. Responses to focal somatic application of 1 mM ACh, current reduction/block with MLA, MEC or both. (A) Focal somatic application of 1 mM ACh produces a fast inward current in a type-1 cell. (B) Scatter plot (left) and associated traces (right) illustrating the effect of 50 nM MLA in the same cell as in (A). (C) Group data for type-1 cells showing the average (% ± S.E.M.) magnitude of peak currents following MLA relative to baseline (15.2 ± 3.7%, $n = 9$). (D) Focal somatic application of 1 mM ACh produces an inward current in a type-2A cell. (E) Scatter plot (left) and associated traces (right) illustrating the effect of sequential application of 50 nM MLA and 5 μM MEC in the same cell as in (D). (F) Group data for type 2A cells showing the average (% ± S.E.M.) magnitude of peak currents following MLA and MLA + MEC relative to baseline (MLA: 27.9 ± 4.6%, $n = 7$; MLA + MEC: 6.7 ± 2.3%, $n = 5$). (G) Focal somatic application of 1 mM ACh produces an inward current in a type-2B cell. (H) Scatter plot (left) and associated traces (right) illustrating the effect of sequential application of 50 nM MLA and 5 μM MEC in the same cell as in (G). (I) Group data for type 2B cells showing the average (% ± S.E.M.) magnitude of peak currents following MLA and MLA + MEC relative to baseline (MLA: 53.9 ± 2.2%, $n = 6$; MLA + MEC: 16.7 ± 3.4%, $n = 6$). Scale bars in (A, B, D, E, G and H) are 100 pA/100 ms.

by 52.6 ± 4.6% whereas peak currents from type-2A cells were reduced by 71.9 ± 5.7% (compare examples in Fig. 1E and H, and F and I). Even though the ACh-evoked responses of the type-2B cells had monophasic kinetics, we hypothesize that the portion of type-2B current blocked by MLA was mediated mainly through α7 receptors. However, we cannot rule out the possibility of other (non-α7) MLA-sensitive channels contributing to the type-2B whole-cell responses.

Type-3 cells ($n = 19$) were unresponsive to ACh application (data not shown) and had moderate firing rates (14.8 ± 3.4 Hz). Ih was present in 92% of these cells and 38.5% showed accommodation. For a summary of the above data, see Table 1.

In order to investigate whether the inward currents induced by focal somatic application of ACh resulted from action potential- or Ca^{2+} channel-dependent neurotransmitter release, we administered 1 μM TTX and 200 μM $CdCl_2$ to type-1 cells (Fig. 3A and B) ($n = 5$) and type-2 cells (Fig. 3C and D) ($n = 5$). In each case there was little or no evidence for a reduction in peak current (type-1: 99.5 ± 9.0%; type-2: 102.7 ± 6.1%).

Table 1
Summary of cell characteristics in accord with response to somatic application of ACh (response type)

Response type	%	ACh-evoked current		Current clamp		
		TTP (ms)	Peak (pA)	FF (Hz)	%Ih	%Accom
Type 1	24	28.4 ± 0.8	138 ± 21.5	7.0 ± 1.0	0	100
Type 2A	33	35.2 ± 4.2	172 ± 25.1	10.5 ± 1.7	23	54.5
Type 2B	21	235.4 ± 28.1	78.3 ± 10.7	27.9 ± 6.9	63	12.5
Type 3	22	–	–	14.8 ± 3.4	92	38.5

%: Percent of cells by type; TTP: time to peak; peak: peak amplitude of response; FF: firing frequency; %Ih: percent showing Ih; %Accom: percent showing accommodating action potentials. Values are presented as mean ± S.E.M. where appropriate.

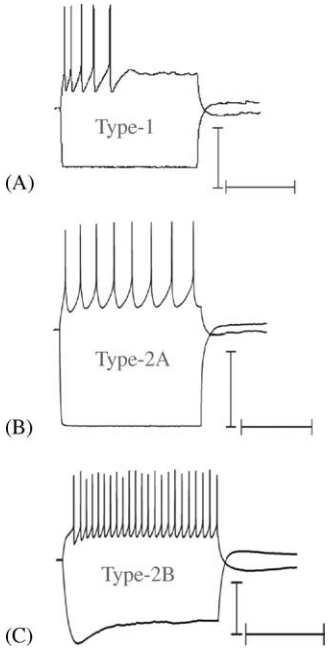

Fig. 2. Current clamp traces showing representative responses to hyper- and depolarization in type-1, type-2A and type-2B cells. (A) Current clamp recording from a type-1 cell showing slow firing and accommodating action potentials with no Ih. (B) Current clamp recording from a type-2A cell showing a moderate firing rate and in this case no Ih. (C) Current clamp recording from a type-2B cell showing fast firing and Ih. Scale bars are 50 mV/0.5 s.

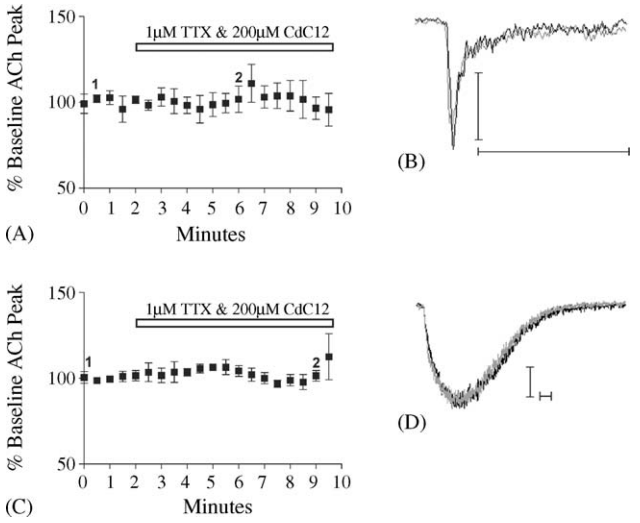

Fig. 3. Application of TTX and $CdCl_2$ did not reduce the magnitude of currents produced by focal somatic application of 1 mM ACh in type-1 or type-2 cells. (A) Scatter plot showing no effect of 1 μM TTX and 200 μM $CdCl_2$ on the amplitude of ACh-evoked currents in type-1 cells. (B) Corresponding current traces from an individual experiment included in (A), where the black trace (corresponding time plotted as #1 in A) is a baseline response and the gray trace (corresponding time plotted as #2 in A) is following 1 μM TTX and 200 μM $CdCl_2$. (C) Scatter plot showing no effect of 1 μM TTX and 200 μM $CdCl_2$ on the amplitudes of ACh-evoked currents in type-2 cells. (D) Corresponding current traces from an individual experiment included in (C), where the black trace (corresponding time plotted as #1 in C) is a baseline response and the gray trace (corresponding time plotted as #2 in C) is following 1 μM TTX and 200 μM $CdCl_2$. Scale bars in (B and D) are 100 pA/100 ms.

This is among the first reports to show direct evidence for functional nicotinic receptors in the MS/DB [10]. We found ∼78% of MS/DB cells have functional nicotinic receptors as indicated by their response to somatic application of 1 mM ACh in the presence of atropine. Previous reports have shown that fast firing cells in the MS/DB are GABAergic and slower firing cells are cholinergic [8,9,20], which together with the present data, suggest that cells exclusively expressing MLA-sensitive nicotinic receptor currents are cholinergic whereas cells that express both MLA-sensitive and resistant currents are GABAergic, cholinergic, or both. The association of specific nicotinic receptor subtypes with identified GABAergic and cholinergic MS/DB neurons may suggest an ability for differential nicotinic modulation of these cell types.

Interestingly, although type-2A and -2B cells contained both MLA-sensitive and MLA-resistant currents, type-2B cells had higher firing rates, a higher percentage showing Ih, and a lower percentage showing accommodation. Because higher firing rates, the presence of Ih and non-accommodating action potential trains are consistent with GABAergic cell firing profiles [8,9,20], our findings suggest that cells with GABAergic firing profiles are likely to contain less MLA-sensitive current than those with cholinergic firing profiles. Inversely, those cells with more MLA-sensitive current are likely to maintain cholinergic-type firing profiles. Our data are further consistent with this idea as type-1 cells, which showed the relatively largest amount of MLA-sensitive current, showed cholinergic-type firing profiles exclusively (slow firing rates, no Ih and accommodating action potential trains).

In situ hybridization [4] and immunocytochemical [10] studies have found evidence for α4, β2 and α7 nAChR subunits in the MS/DB. Because it has been shown that low concentrations of MLA are selective for α7 nicotinic receptors [13], and that there is little evidence for MS/DB nicotinic receptor subtypes other than α7, α4 and β2, it appears the currents in the present report involve activation of α7 (MLA-sensitive) and possibly α4β2 (MLA-resistant) nicotinic receptor subtypes. Additional evidence for the presence of both α7 and non-α7 nAChR in type-2A cells comes from a recent study utilizing a new antagonist TMPH [18], which produces a readily reversible block of α7 receptors and long-term inhibition of non-α7 nAChR. This study showed that TMPH spares the rapid transient portion of type-2A responses and has a prolonged effect on the non-α7 component of the responses.

Our results are in general agreement with those reported by Henderson et al. [10], despite the fact that these authors used alternative neuronal identification procedures. Henderson et al. [10] reported in rats and mice that α7 receptors were expressed in all cells with cholinergic firing profiles and in 10% of GABAergic cells as identified with an in vivo marker for parvalbumin. Also, these authors reported non-α7 receptors in 50% of GABAergic neurons. In the present report, cells

were identified as cholinergic or GABAergic based on firing profiles and the presence of Ih [8,9]. Under the assumption that cells having firing rates ≥10 Hz with Ih are GABAergic and cells having firing rates <10 Hz with no Ih are cholinergic, our data show that ∼60% of GABAergic cells did not respond to ACh (type-3) and that ∼40% had both α7 and non-α7 currents (type-2A and B). In cholinergic cells, ∼50% showed evidence for α7 and non-α7 currents (type-2A and B) and ∼50% showed evidence for α7 alone (type-1).

Our results are inconsistent with those reported by Wu et al. [23] in that we show: (1) MS/DB cells respond to ACh application with MLA-sensitive currents indicating the presence of α7 subtype nicotinic receptors; and (2) responses to ACh were not affected by application of TTX and $CdCl_2$ but were completely blocked by either MLA or a combination of MLA and MEC, suggesting these currents were produced by direct activation of somatic or somato-dendritic nicotinic receptors. Our results are similar to observations on nicotinic receptors in hippocampal interneurons which also are unaffected by TTX and $CdCl_2$ [6,15]. The incongruity between our results and those reported by Wu et al. [23] could have resulted from any number of methodological differences. However, one substantial difference between the studies involves agonist application techniques. In our study, agonist applications were made with focal somatic "puffs" of ACh with durations of 5–30 ms. In contrast, responses recorded by Wu et al. [23] were evoked mostly with bath and Y-tube applied nicotine, using durations ranging from 10 s to 1 min. It is known that nicotinic receptors are rapidly desensitizing; therefore, the differences in agonist application methods could easily account for the differences in the findings between these studies.

These findings are among the first to report evidence for potential substrates that might mediate direct activation of nicotinic receptors in the MS/DB [10]. Previous studies have argued that activation of MS/DB nicotinic receptors occurs via presynaptic events involving action potential-dependent neurotransmitter release [23]. In contrast, the findings in the present report and those reported by Henderson et al. [10] suggest that whole-cell currents evoked by focal somatic ACh applications are produced by direct activation of nicotinic receptors on MS/DB cells. Our data, in agreement with Henderson et al. [10], suggest that MS/DB nicotinic receptors include both α7 and non-α7 subtypes and that their expression is correlated with firing frequency and the presence of Ih. Understanding these mechanisms may prove useful for targeting therapeutic approaches to diseases that involve cholinergic hypofunction such as Alzheimer's disease (AD) or age-related memory disorder. Further, α7 receptor activation is neuroprotective in several models [1,14,16], but the utility of this approach for treating at-risk neurons in conditions such as AD depends on the expression of the receptor by the at-risk neurons. Basal forebrain cholinergic neurons are preferentially lost in AD over GABAergic neurons [17], and it appears from the present work that in the MS/DB they consistently express α7 receptors. Therefore, these receptors appear to be potential therapeutic targets for protecting virtually all of the MS/DB cholinergic neurons and likely some GABAergic neurons as well.

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