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# COMMENTARY

# Gates and filters: unveiling the physiological roles of nicotinic acetylcholine receptors in dopaminergic transmission

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Neuronal nicotinic acetylcholine receptors (nAChRs) in the brain have been enigmatic players on the cerebral stage. As ligand-gated ion channels they were expected to mediate fast cholinergic transmission, yet their influence appears to be modulatory. Two reviews in this issue of the *BJP* consider the relationship between nAChRs and endogenous ACh, with respect to the modulation of dopaminergic signalling. In his review, Maskos posits that in midbrain dopamine neurons, somatodendritic nAChRs activated by cholinergic inputs from the pedunculopontine tegmental nucleus (PPTg) and laterodorsal tegmental nucleus (LDTg) serve as a 'gate' that facilitates the switch to burst firing. In the terminal field, Exley and Cragg argue that nAChRs function as a 'presynaptic filter' to enhance the contrast between single and repetitive spike firing. Thus somatodendritic and presynaptic nAChRs exert subtle and complementary influences in responding to cholinergic inputs.
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**Abbreviations:** LDTg, laterodorsal tegmental nucleus; nAChR, nicotinic acetylcholine receptor; PPTg, pedunculopontine tegmental nucleus; TANs, tonically active neurons; VTA, ventral tegmental area

Initially, the existence of nicotinic acetylcholine receptors (nAChRs) in the brain was controversial: nicotine was recognized to be the principal psychoactive constituent in tobacco, charged with sustaining tobacco addiction, yet its molecular target in the CNS was obscure (Clarke, 1992). Now, molecular cloning has identified 6α (α2–α7) and 3β (β2–β4) nAChR subunits expressed in the mammalian brain (Gotti *et al*., 2006), which combine to form numerous heteromeric nAChRs (composed of α and β subunits) to complement homomeric α7 nAChRs. Surely this diversity should be matched by an abundance of nicotinic currents recorded from CNS neurons. Indeed, nicotinic currents are demonstrable in many types of neuron, providing evidence for somatodendritic nAChRs. But, in all but a few cases, it has been difficult to show that such nAChRs are postsynaptic to cholinergic inputs, encouraging the view that many nAChRs respond to volume transmission in the cholinergic system (Descarries *et al*., 1997; Zoli, 2000). It was also evident from early neurochemical studies that nAChRs are commonly located on presynaptic terminals where they can elicit neurotransmitter release *in vitro* (Wonnacott, 1997). These features have prompted the view that nAChRs in the brain are predominantly modulatory, influencing neuronal excitability and regulation at the somatodendritic level and locally regulating transmitter release (Role and Berg, 1996; Dajas-Bailador and Wonnacott, 2004).

Modulation of the dopaminergic system by nAChRs has received a lot of attention, reflecting the relatively high densities of presynaptic and somatodendritic nAChRs, and the importance of the mesolimbic and nigrostriatal systems for the rewarding and locomotor activating properties of nicotine. Dopamine neurons express numerous nAChR subunits and subtypes. In rodents, biochemical, pharmacological and genetic strategies have identified presynaptic nAChRs comprising α4β2, α4α5β2, α6β2, α6β2β3 and α6α4β2β3 subunit combinations (Grady *et al*., 2007), whereas $(\alpha4)_2\alpha5(\beta2)_2$ and $\alpha4\alpha6\alpha5(\beta2)_2$ (and a few α7 nAChRs) occur somatodentritically (see Wonnacott *et al*., 2005). *What is the physiological significance of this distribution and this diversity?* Although nicotine and other agonists can activate presynaptic and somatodendritic nAChRs, the physiological significance of these nAChRs in relation to endogenous cholinergic signalling has been somewhat neglected.

Midbrain dopamine neurons exhibit two distinct firing patterns: tonic single spike activity (the regular firing of action potentials, constituting a rhythmic pacemaker function) and burst spike firing (a phasic pattern of bursts of

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action potentials; Goto *et al*., 2007). Tonic firing sustains dopamine release in the terminal fields, resulting in a tonic concentration of ~10 nM in the striatum. The shift to burst firing provokes greatly increased dopamine release, resulting in transient local peaks of extracellular dopamine (see Goto *et al*., 2007). This change in the firing pattern is associated with unexpected rewards and is central to reinforcing behaviours.

The principal cholinergic inputs to midbrain dopamine neurons are from the pedunculopontine tegmental nucleus (PPTg) and the laterodorsal tegmental nucleus (LDTg) (Winn, 2006). Here Maskos (2008) reviews the current understanding of the anatomical and physiological significance of the PPTg and LDTg and speculates on their significance for the nicotinic modulation of dopamine system. These cholinergic inputs synapse onto dopaminergic cell bodies, consistent with at least some somatodendritic nAChRs on these neurons undertaking synaptic nicotinic cholinergic transmission. Such cholinergic stimulation regulates the switch from tonic activity to burst firing: the switch to burst firing is driven by glutamatergic inputs and, in the ventral tegmental area (VTA) at least, can be augmented by presynaptic α7 nAChRs on glutamate afferents (Mansvelder and McGehee, 2000; Schilstrom *et al*., 2003). However, cholinergic nicotinic transmission from the PPTg/LDTg is proposed to serve as an essential 'gate' that permits this switch to occur: the nicotine-induced switch to burst firing is markedly diminished in knockout mice lacking the β2 nAChR subunit and restored by targeted expression of the β2 subunit in the VTA, implicating heteromeric nAChRs located on dopaminergic (and GABAergic) cell bodies and dendrites in the VTA (Mameli-Engvall *et al*., 2006).

Thus, cholinergic nicotinic innervation of the VTA makes a vital contribution to the mechanisms of nicotine reinforcement and this nicotinic gateway may have a more general role in regulating goal-directed behaviours, or determining individual differences in drug abuse liability (Fagen *et al*., 2007).

So if somatodendritic nAChRs control the firing pattern of dopamine neurons and that determines the release of dopamine in the terminal regions, what is the physiological purpose of presynaptic nAChRs on dopamine terminals? The ability of such nAChRs to promote dopamine release in *in vitro* preparations devoid of somatodendritic regions and lacking intrinsic firing patterns has led to the perhaps naive view that this is simply their role *in vivo*. The use of fast cycling voltametry for monitoring dopamine release with high temporal and spatial resolution from striatal slices in which tonic and burst firing patterns can be reproduced, together with modelling the cholinergic tone that exists in the striatum, has allowed nAChR function under pseudo-physiological conditions to be interrogated (Zhou *et al*., 2001; Rice and Cragg, 2004). New insights into the significance of presynaptic nAChRs from such studies are the subject of the review by Exley and Cragg (2007).

The endogenous agonist for presynaptic nAChRs on dopamine terminals is provided by the sparse, large aspiny cholinergic interneurons of the striatum. These tonically active neurons (TANs) release ACh from varicosities that mostly do not make synaptic contacts, so that ACh acts by volume transmission (Descarries *et al*., 1997). A reward-related cue that switches the dopamine neurons to burst firing produces a complementary silencing of the TANs' activity; hence, increased dopamine release is paralleled by a fall in ACh. It is proposed that presynaptic nAChRs serve as dynamic detectors of ACh concentration, enhancing the contrast between tonic and burst firing. This role is revealed by application of β2 subunit-selective nicotinic antagonists to block the presynaptic nAChRs on dopamine terminals (Rice and Cragg, 2004). Through the influence of firing pattern on whether presynaptic nAChRs facilitate or inhibit dopamine release, the authors propose that these nAChRs serve as a 'presynaptic filter' (Exley and Cragg, 2008). The need for multiple heteromeric nAChR subtypes is presently unclear but one can speculate that subtle differences in the regulation of their expression or trafficking, or rates of desensitization or recovery, could enhance the exquisite fine-tuning that the presynaptic nAChRs are proposed to provide.

It is indubitable that nAChRs are not expressed in the brain solely to report the presence of the exogenous substance nicotine; their primary function is to respond to cholinergic signalling. The deficit in our understanding of how nAChRs contribute to complex physiological scenarios is now beginning to be redressed, with fascinating revelations at both ends of the neuron.

## References

Clarke PB (1992). The fall and rise of neuronal alpha-bungarotoxin binding proteins. *Trends Pharmacol Sci* **13**: 407–413.

Dajas-Bailador F, Wonnacott S (2004). Nicotinic acetylcholine receptors and the regulation of neuronal signalling. *Trends Pharmacol Sci* **25**: 317–324.

Descarries L, Gisiger V, Steriade M (1997). Diffuse transmission by acetylcholine in the CNS. *Prog Neurobiol* **53**: 603–625.

Exley R, Cragg S (2008). Presynaptic nicotinic receptors: a dynamic and diverse filter of striatal dopamine neurotransmission. *Br J Pharmacol* **153** (Suppl 1): S283–S297 (this issue).

Fagen ZM, Mitchum R, Vezina P, McGehee DS (2007). Enhanced nicotinic receptor function and drug abuse vulnerability. *J Neurosci* **27**: 8771–8778.

Goto Y, Otani S, Grace AA (2007). The Yin and Yang of dopamine release: a new perspective. *Neuropharmacology* **53**: 583–587.

Gotti C, Zoli M, Clementi F (2006). Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol Sci* **27**: 482–491.

Grady SR, Salminen O, Laverty DC, Whiteaker P, McIntosh JM, Collins AC *et al.* (2007). The subtypes of nicotinic acetylcholine receptors on dopaminergic terminals of mouse striatum. *Biochem Pharmacol* **74**: 1235–1246.

Mameli-Engvall M, Evrard A, Pons S, Maskos U, Svensson TH, Changeux JP *et al.* (2006). Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors. *Neuron* **50**: 911–921.

Mansvelder HD, McGehee DS (2000). Long-term potentiation of excitatory inputs to brain reward areas by nicotine. *Neuron* **27**: 349–357.

Maskos U (2008). The tegmentum as a neglected master modulator of the dopaminergic system. *Br J Pharmacol* **153** (Suppl 1): S438–S445 (this issue).

Rice ME, Cragg SJ (2004). Nicotine amplifies reward-related signals in the striatum. *Nat Neurosci* **7**: 583–584.

Role LW, Berg DK (1996). Nicotinic receptors in the development and modulation of CNS synapses. *Neuron* **16**: 1077–1085.

Schilstrom B, Rawal N, Mameli-Engvall M, Nomikos GG, Svensson TH (2003). Dual effects of nicotine on dopamine neurons mediated by different nicotinic receptor subtypes. *Int J Neuropsychopharmacol* **6**: 1–11.

Winn P (2006). How best to consider the structure and function of the pedunculopontine tegmental nucleus: evidence from animal studies. *J Neurol Sci* **248**: 234–250.

Wonnacott S (1997). Presynaptic nicotinic receptors. *Trends Neurosci* **20**: 92–98.

Wonnacott S, Sidhpura N, Balfour DJK (2005). Nicotine: from molecular mechanisms to behaviour. *Curr Op Pharmacol* **5**: 53–59.

Zhou FM, Liang Y, Dani JA (2001). Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. *Nat Neurosci* **4**: 1224–1229.

Zoli M (2000). Distribution of cholinergic neurons in the mammalian brain with reference to their special relationship with neuronal nicotinic acetylcholine receptors. In: Clementi F, Fornasari D, Gotti C (eds). *Neuronal Nicotinic Receptors.* pp 13–30. Springer-Verlag.