Frequency-dependent modulation of dopamine release by nicotine and dopamine D_1 receptor ligands: an in vitro fast cyclic voltammetry study in rat striatum

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Abstract
Nicotine is a highly addictive drug and exerts this effect partially through the modulation of dopamine release and increasing extracellular dopamine in regions such as the brain reward systems. Nicotine acts in these regions on nicotinic acetylcholine receptors. The effect of nicotine on the frequency dependent modulation of dopamine release is well established and the purpose of this study was to investigate whether dopamine D_1 receptor (D_1R) ligands have an influence on this. Using fast cyclic voltammetry and rat corticostriatal slices, we show that D_1R ligands are able to modulate the effect of nicotine on dopamine release. Nicotine (500nM) induced a decrease in dopamine efflux at low frequency (single pulse or 5 pulses at 10Hz) and an increase at high frequency (100Hz) electrical field stimulation. The D_1R agonist SKF-38393, whilst having no effect on dopamine release on its own or on the effect of nicotine upon multiple pulse evoked dopamine release, did significantly prevent and reverse the effect of nicotine on single pulse dopamine release. Interestingly similar results were obtained with the D_1R antagonist SCH-23390. In this study we have demonstrated that the modulation of dopamine release by nicotine can be altered by D_1R ligands, but only when evoked by single pulse stimulation, and are likely working via cholinergic interneuron driven dopamine release.

1. Introduction
Dopaminergic signaling is implicated in many behaviors including drug addiction. Reward-related signaling for both primary reinforcers and conditioned stimuli is conveyed by mesostriatal dopamine release by phasic bursts of action potentials, rather than single-spike or tonic activity [1]. A long-held view of nicotine in addiction is that its properties are mediated by increased dopamine release. On the other hand there is now evidence that nicotine modulates and enhances the contrast of dopamine signals associated with behavioral cues [2]. It has been demonstrated that nicotine shifts neurons from tonic to burst firing modes [3, 4] and, it potentially desensitizes nicotinic acetylcholine receptors (nAChR) so rapidly that tonic ACh activation is blocked and evoked dopamine release is potently inhibited [2]. While desensitization of β2-subunit containing nAChRs attenuates dopamine release evoked by tonic firing frequencies, nicotine does facilitate dopamine release from stimuli emulating phasic burst-like firing frequencies [5, 6].

Recently Threlfell et al., (2012) and Cachope et al., (2012) have used a combination of electrophysiological recordings and optogenetic techniques to investigate a presynaptic mechanism that triggers dopamine release directly and thereby bypassing activity in dopamine neurons directly [7,8]. Activation of cholinergic interneurons (ChI) by flashes of light caused dopamine release via activation of nicotinic receptors on dopamine axons. More recently, Wang and co-workers showed that nicotine could reduce the ChI-induced depletion of the dopamine vesicular pool by suppressing the ChI pathway and that following suppression of this pathway nicotine can facilitate dopamine release during sustained burst local field electrical stimulation in the striatum, suggesting an important role for ChI [9]. Dopamine transmission in the brain utilizes an auto-regulatory system by which dopamine D_2-like receptor (D_2R) activation will inhibit the further release of dopamine and modulate uptake into the pre-synaptic cell. Although this functionality is well described, considerably less attention has been paid to the role of the dopamine D_1-like receptor (D_1R). Contrary to the D_2R, D_1Rs are not located on dopamine axons and activation of the D_1R will not directly regulate the release of dopamine. For example, neither the D_1R agonists 6-Cl-APB or SKF-38393 nor the D_1R antagonist SCH-23390 altered single pulse dopamine release in brain slices on their own [10]. However Stouffer et al. (2011), have shown that the D1R antagonist SKF-83566 can enhance evoked dopamine release detected by fast cyclic voltammetry (FCV) by inhibiting the dopamine transporter [11].

Appropriate responses to primary reinforcers and conditioned stimuli, including pursuit of reward or avoidance of aversive experience all require functional striatal circuits. Although many neurotransmitters participate in striatal circuitry, dopamine and acetylcholine are critically important players. D_1Rs are located on striatal GABAergic medium spiny neurons and interneurons, which form synaptic connections with ChIs and have a prominent influence over ChI activity. In addition, ChIs express low levels of D_1Rs (see for review Lim *et al.* [12]). In the present work, we determined the effect of D_1R ligands on the modulating effect of nicotine on striatal dopamine release during tonic and phasic associated patterns of dopaminergic pathway activity. We mimicked these fast temporal processes by electrical stimulation using a bipolar stimulation electrode and stimuli at specific frequencies in rat striatal slices in combination with a high temporal resolution electrochemical technique, FCV [13]. Furthermore, the impact of this research on the characterization of behavioral sensitization is discussed.

2. Materials and Methods

2.1. Brain slice preparation

All experiments used naïve adult male Wistar Unilever Harlan (WUH) rats of 100-150 g (Harlan, UK) and experimental procedures were carried out according to the regulations of the Animal Research Ethics Committee of NUIM and national legislation. The animals were killed by decapitation, using a guillotine. Brains were dissected and directly placed in ice-cold Krebs-Ringer Buffer, KRB (in mM): 121 NaCl, 2 KCl, 25 $NaHCO_3$, 1.2 $MgSO_4$, 11 D-(+)-glucose, 1.2 KH_2PO_4 (Gibco-Invitrogen, the Netherlands), with modifications as used during experiments: 2.4 $CaCl_2$ and 22 D(+)-glucose. The buffers were gassed with 95% O_2/5% CO_2 (BOC gasses, Ireland) before and during commencing the slicing procedure. For striatal recordings, the brain was blocked sagittally to split both hemispheres and cut along the midline between coordinates +1.7 – +0.2 mm relative to Bregma. The tissue block was sliced (350 µm) using a vibratome (Campden Instruments, UK).

2.2. Fast Cyclic Voltammetry (FCV) recordings

Voltammetric recordings in dorsal striatum slices were performed as previously described [14]. A three-electrode setup was used consisting of a carbon fiber electrode, CFE (diameter 5 µm. length 30-60 µm, KationScientific, USA) for current recordings, and two Ag/AgCl auxiliary and reference electrodes. All electrodes were connected to a head-stage amplifier (Millar voltammeter probe, 2x amplification) and a Millar-potentiostat (PD systems, UK, kindly donated by Dr. Julian Millar). A triangular waveform from 0 to -1.0 to +1.4 to -1.0 and back to 0 V vs. Ag/AgCl was used at a scan rate of 480 V/s. The sampling rate was 4 Hz and data were digitized using an A/D-converter (Powerlab 4/20, ADInstruments, UK). Bipolar tungsten electrodes (100 µm apart; 0.1 MΩ, Molecular Devices Inc, USA) were used for electrical stimulation. The bipolar electrodes were placed in the slice (50 µm below the surface), approximately 100 µm from the tip of the CFE also 50 µm below the surface. Monophasic stimulation pulses (100 µs width, 10 V amplitude) generated by a NeuroLog stimulator (NL-800, Digitimer, UK) with an isolation unit (SIU5, Grass Technologies) were used to evoke dopamine release. Dopamine was evoked at either single pulse, low frequency (5p/10Hz) or high frequency (5p/100Hz) stimulation every 5 min. The electrodes were placed into the dorsal lateral region of the striatum where transient dopamine release was monitored, and the position was adjusted to a site where robust single pulse dopamine release was achieved. All electrodes were calibrated in KRB (as described in detail previously [15]) in the range 0.05 to 1 µM dopamine. Evoked single pulse dopamine release was calculated to be in the range 0.11 to 0.18µM dopamine during the course of the experiments.

2.3. Data analyses

Chart software (v5.2, AD Instruments, UK) was used for data analysis. Amplitudes (voltages, V) were converted to currents (amperage, A) and corrected for gain settings. Graphs and statistical analyses were performed using PRISM software (GraphPad, USA). Multiple pulse stimulation data was obtained in the same recording site to that of the single pulse data. Therefore all data are presented as mean±s.e.m peak single pulse dopamine release. Statistical significance was determined by one-way analysis of variance (ANOVA) or Student's t-test, as appropriate. A difference was considered significant at $p<0.05$. In Fig 1a single pulse peak dopamine release was measured for 20 min prior to nicotine application and the average of these values were taken as 100%. In Fig 1b, 1c and 2, peak 5p/10Hz and 5p/100Hz evoked dopamine release is presented as a % of peak single pulse dopamine release.

2.4. Compounds

(-)-Nicotine ditartrate dihydrate was purchased from Acros Organics (Geel, Belgium). All other drugs and chemicals used in this study were obtained from Sigma-Aldrich (Zwijndrecht, the Netherlands) except where specifically noted. SKF-38393 and SCH-23390 were superfused for 30 min before test stimuli.

3. Results

As shown previously addition of nicotine (500 nM) to brain slices decreased single pulse induced dopamine release by 32%. The effect of nicotine on dopamine release was rapid and its maximal effect was achieved by 10 min (Fig 1a). As the effects of nicotine on dopamine release are dependent on the firing frequency of dopaminergic neurons and cholinergic interneurons (see Introduction) we used a stimulation protocol of 5 pulses at 10 Hz (5p/10Hz) and 5 pulses at 100 Hz (5p/100Hz). Peak dopamine release measured by either single pulse, low frequency (5p/10Hz) or high frequency stimulation (5p/100Hz) was not significantly different (Fig 1b, black lines). The addition of nicotine significantly decreased dopamine release when evoked by either single pulse or low frequency stimulation (100% vs. 64±8%, $p<0.01$, and 118±12% vs. 58±14%, $p<0.01$, respectively; Fig 1b). However, in the presence of nicotine, dopamine release evoked by high frequency stimulation was significantly increased (116±13% vs. 215±15%, $p < 0.01$; Fig 1b).

We have previously shown that nicotine-induced behavioral sensitization can be attenuated by D_1R ligands [16]. We therefore investigated the effect of D_1R ligands on stimulated dopamine release at low and high frequencies (see Discussion). Perfusion of the D_1R agonist SKF-38393 (1 µM) for 25 min had no significant effect on dopamine release evoked by the different stimuli ([$F(2, 8)=0.8763$; $p=0.4528$], grey bars, Fig 1c). When slices were pre-incubated with SKF-38393, nicotine (500nM) caused a significant decrease in dopamine release evoked at 5p@10Hz ([$F(2, 8)=30.84$; $p=0.0002$]), and a significant increase in dopamine release evoked at 5p@100Hz ([$F(2, 7)=18.39$; $p=0.0016$]) which was comparable to that observed for nicotine alone (dotted lines). However, SKF-38393 blocked the inhibitory effect of nicotine on single pulse evoked dopamine release (Fig 1c).

Next we examined the effect of the prototypical D_1R antagonist SCH-23390 on stimulated dopamine release. SCH-23390 (1 µM) caused a small, but not

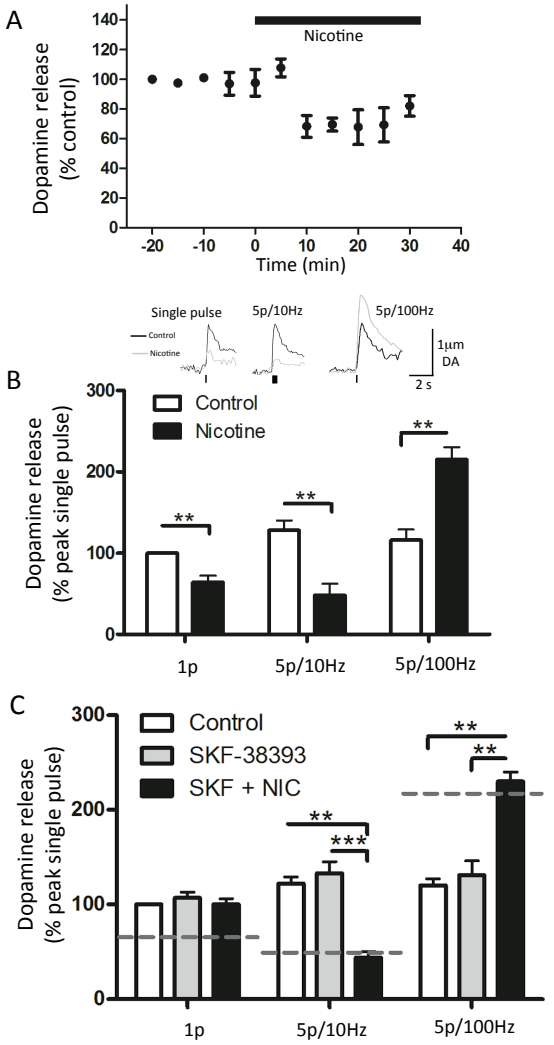

Figure 1. **Modulation of evoked dopamine release by nicotine and SKF-38393 depends on firing pattern**
(a) Effect of bath application of nicotine (500 nM) on single pulse stimulated dopamine release every 5 min. Nicotine was added to the bath at time 0. (b) Nicotine decreased dopamine release at single pulse and low frequency (5p/10H) stimulations and increased dopamine release at high frequency stimulations (5p/100Hz; control, white bars, nicotine, black bars). Upper traces show representative voltammetric responses of dopamine release before (black lines) and after bath application of nicotine (grey lines) at the different stimulation frequencies. (c) Summary of the effect of the D_1R agonist SKF-38393 (1 µM) alone and in combination with nicotine on stimulated dopamine release. SKF-38393 (grey bars) had no significant effect on dopamine release evoked by the different stimuli. Black bars indicate slices that were pre-incubated with SKF-38393 and nicotine (500 nM). SKF-38393 blocked the inhibitory effect of nicotine applied alone on single pulse evoked dopamine release. There was a significant decrease in dopamine release evoked at 5p/10Hz and a significant increase in dopamine release evoked at 5p/100Hz when compared to nicotine alone (dotted lines represents nicotine alone, see panel (b)). In (a) and (b), all data is the mean±s.e.m, n=4-5. Unpaired two-tailed t-test, $^{**}p<0.01$. In (c), *Post hoc* Bonferroni's, $^{**}p<0.01$, $^{***}p<0.001$; n=4-5.

significant increase in dopamine release at all stimulation conditions ([$F(2, 9)=3.610$; $p=0.0706$], grey bars, Fig 2a). SCH-23390 also significantly blocked the effect of nicotine on dopamine release evoked by a single pulse, and increased dopamine release compared to controls, but did not alter its effect on dopamine release evoked by 5p/10Hz or 5p/100Hz stimulation (black bars, Fig 2a). These results were obtained regardless as to whether the antagonist was applied before or after nicotine application; no significant effect of treatments was observed following pre-incubation with nicotine compared to their respective controls (unpaired two-tailed t-test, $p>0.05$, Fig 2b).

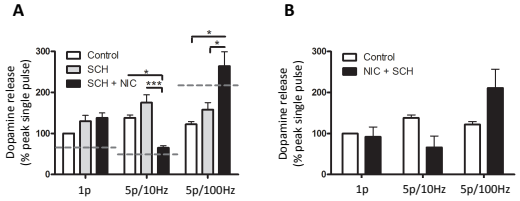

Figure 2. **Effect of the D_1R antagonist, SCH-23390 alone and in combination with nicotine on stimulated dopamine release**
(a) Slices were incubated with SCH-23390 (1 µM) for 30 min and dopamine release was evoked by single pulse stimulation (left bars), 5p/10Hz (middle) or 5p/100Hz (right bars). SCH-23390 had no significant effect on dopamine release at all stimulations. Black bars indicate slices that were pre-incubated with SCH-23390 and nicotine (500 nM). SCH-23390 significantly blocked the effect of nicotine on dopamine release evoked by a single pulse, but did not alter nicotine's effect on dopamine release evoked by 5p/10Hz or 5p/100Hz (black bars). Dotted line represents nicotine control level (see Fig 1b; *post hoc* Bonferroni's, $^{*}p<0.05$; $^{***}p<0.001$; $n=4$). (b) The results shown in (a) were obtained regardless as to whether the antagonist was applied before or after nicotine application; Slices were first incubated with nicotine for 30 min and SCH-23990 (1 µM) added. No significant effect of treatment was observed following pre-incubation with nicotine compared to their respective controls (unpaired two-tailed t-test, $p>0.05$, n=4).

4. Discussion

This study has demonstrated that nicotine inhibits dopamine release stimulated by low frequencies and increases dopamine release at high frequency stimulation as has previously been described by others [5,6,7,8.17]. Thus, whereas nicotine-induced desensitization decreases and inhibits dopamine release at low activity, the inhibition is compensated during burst firing by short-term facilitation. Most importantly we have shown for the first time that both inhibition (SCH-23390) and stimulation (SKF-38393) of the D_1R profoundly attenuated the effect of nicotine on presynaptic activity.

For many years it was believed that dopamine release from the ascending pathway was modulated by nicotine [2, 5, 6]. However, this conclusion was made from studies based on stimulation without considering a possible contribution of the ChI-driven dopamine release. Recent advances in the field of neurochemistry now explain the bidirectional effect of nicotine on stimulated dopamine release in the dorsal striatum. Whilst it has recently been elegantly shown that dopamine release driven by action potential firing in dopaminergic axons alone is insensitive to nicotine, nicotine selectively blocks ChI-induced dopamine release [7]. Nicotine selectively blocked the ChI pathway by desensitizing α6β2*nAChRs on the dopaminergic terminals, which caused the inhibition of dopamine release following a single pulse (representing low

frequency tonic firing). Nicotine can also cause short-term facilitation of dopamine release at the second and the third pulses in the 20 Hz burst of stimuli (mimicking high-frequency phasic firing) because blockade of the ChI pathway reduced the depletion of the dopamine vesicle pool at the first pulse in a train [7].

A long-held view of psychostimulant addiction (for example by nicotine, cocaine, or amphetamine) is that the reinforcing properties are mediated by an increase in dopamine levels, especially within the striatum (*e.g.* Di Chiara and Imperato [18]). Paradoxically, it has been reported in human, animal and cell based studies that nicotine administration desensitizes nAChR on dopaminergic neurons [19] and suppresses striatal dopamine release evoked by single action potentials [2]. This phenomenon was further studied in brain slices using fast cyclic voltammetry, offering high spatial and high temporal resolution. A bidirectional effect of nicotine on dopamine release has been demonstrated; *i.e.* when stimulating electrically at a low frequency (representing tonic release) nicotine decreased dopamine release, when stimulating at high frequency (representing phasic release) nicotine increased dopamine release [5, 6]. Our study confirmed these findings of the effect of nicotine on stimulated dopamine release.

The present study investigated the pharmacological "modification" of nicotine-induced "frequency-dependent-signalling" on dopamine release. The study examined the effect of the D_1R agonist SKF-38393 and the D_1R antagonist SCH-23390 on nicotine's biphasic modulation of dopamine release. SKF-38393 or SCH-23390 alone were ineffective in altering stimulated dopamine release, which can be explained by the fact that the D_1R is localized post-synaptically on GABAergic and ChI and therefore may not directly affect dopamine release. This finding is also in agreement with previous literature [10]. For the first time, this study has shown that SKF-38393 and SCH-23390 selectively affect nicotine-induced frequency-dependent dopamine release. It was found that pre-treatment with either D_1R ligand significantly blocked or attenuated nicotine's effect on single pulse, but not at multiple pulse (high frequency) stimulated dopamine release. A potential mechanism for this interaction between the D1Rs and nAChRs might be an intracellular pathway between these two receptor types. In a previous study, we provided data suggesting a functional link between the nAChR and D1R through a cAMP-dependent pathway downstream of the D1R [16]. However, nAChR stimulation may not only facilitate dopamine release but may also up-regulate the expression of D1Rs. Interestingly Komal et al., 2015 [20] have only recently demonstrated an interaction between cholinergic and dopaminergic systems through protein kinase A. Further studies are needed to elucidate the possibility of an intracellular pathway between the nAChR and D1R.

In addition the effects observed with both agonist and antagonist might well be explained by the reported partial agonism exerted by SKF-38393. Both Brewster et al., (1990) [21] and Heidenreich et al., (1995) [22] have previously presented some evidence for a partial agonist effect of SKF-38393 on D1Rs. SCH-23390 is likely to be a full and selective D1R-like antagonist although it does show high efficacy at serotonergic 5-HT2c receptors [23]. The present study also suggests that D_1R ligands do not affect action potential dependent dopamine release. However, it must be considered if single or multiple nAChR subtypes play this essential and complex role in the bidirectional effect of nicotine on dopamine release [24]. Besides desensitization of the β2-containing nAChR, it has been suggested that there is an important role for functional α7*nAChRs [25] and this may depend upon endogenous ACh levels evoked by the stimulation.

As nicotine preferentially filters the dopamine signal resulting from lower tonic activity, it could enhance the dopamine response due to salient stimuli that evoke burst firing [26]. Such contrast enhancement between tonic and phasic activity might help to elucidate the underlying mechanism of nicotine-induced behavioral sensitization and the development of addiction disorders. Recently we reported the involvement of D_1R and showed that SCH-23390 attenuated nicotine-induced behavioral sensitization [16]. Muscat and colleagues have also studied the effect of amphetamine-induced behavioral sensitization on *ex vivo* dopamine release and observed a differential effect, unaffected single pulse but attenuated multiple pulse induced dopamine release [27]. Moreover, it has been reported that the actions of released dopamine on other neuronal projections are also based on input frequency [28].

5. Conclusions

In summary, as has previously been described, nicotine depressed or facilitated dopamine release depending on the stimulation pattern. These modulatory effects of nicotine on tonic and phasic dopamine release might exert a profound influence on activity-dependent neurotransmission and subsequent synaptic plasticity. This study showed for the first time that D_1R ligands can filter or gate the dopamine release modulated by nicotine. Such contrast enhancement between tonic and phasic activity may help to elucidate the underlying effects of nicotine and D_1R on behavioral sensitization, or other behavioral outcomes permissive for substance use. The present data should encourage further research into this field.

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6. References

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