Brief Communications

Nicotinic α_7 Receptors as a New Target for Treatment of Cannabis Abuse

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Increasing use of cannabis makes the search for medications to reduce cannabis abuse extremely important. Here, we show that homomeric α_7 nicotinic receptors are novel molecular entities that could be targeted in the development of new drugs for the treatment of cannabis dependence. In rats, systemic administration of the selective α_7 nicotinic acetylcholine receptor antagonist methyllycaconitine (MLA), but not the selective heteromeric non-α_7 nicotinic acetylcholine receptor antagonist dihydrobetaerythroidine, (1) antagonized the discriminative effects of δ-9-tetrahydrocannabinol (THC), the main active ingredient in cannabis, (2) reduced intravenous self-administration of the synthetic cannabinoid CB1 receptor agonist WIN55,212-2 [(*R*)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)-methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone, mesylate salt], and (3) decreased THC-induced dopamine elevations in the shell of the nucleus accumbens. Altogether, our results indicate that blockade of α_7 nicotinic receptors reverses abuse-related behavioral and neurochemical effects of cannabinoids. Importantly, MLA reversed the effects of cannabinoids at doses that did not produce depressant or toxic effects, further pointing to α_7 nicotinic antagonists as potentially useful agents in the treatment of cannabis abuse in humans.

Key words: **abuse; acetylcholine receptor; cannabinoids; dopamine; behavior; nucleus accumbens**

Introduction

Cannabis abuse is a widespread phenomenon in western societies, especially among teenagers and young adults. Although physical dependence may be mild, psychological dependence to cannabis may be strong and require medical treatment. Thus, the discovery of new molecular tools to reduce the psychotropic and rewarding effects of cannabis is of primary importance for producing effective therapies.

The cholinergic system could be a possible target for new medications for cannabis abuse. Nicotinic acetylcholine (nACh) receptors are involved in cognition, are highly expressed, as are cannabinoid CB1 receptors, in the hippocampus, and play a role in the cognition-impairing effects of the main psychoactive ingredient of cannabis, δ-9-tetrahydrocannabinol (THC) (Lichtman et al., 2002). nACh receptors are also expressed, as are CB1 receptors, in the mesolimbic dopamine system. Several findings suggest that they play an important role in brain reward processes (Dani et al., 2001) and that cholinergic and endocannabinoid systems interact in modulating reward-related processes (Lichtman et al., 2002; Fattore et al., 2007).

Neuronal nACh receptors can be subdivided into α-bungarotoxin-sensitive or homomeric α_7 nACh receptors formed by five α_7 subunits and α-bungarotoxin-insensitive or heteromeric non-α_7 nACh receptors formed by combinations of different α and β subunits, among which the most common is the $\alpha_4\beta_2$ combination (McGehee and Role, 1995). In the dopaminergic mesolimbic system, a major circuit in the mediation of natural and drug reward, non-α_7 nACh receptors are present both in the ventral tegmental area (VTA), where they are localized on and can directly activate dopaminergic neurons (Mansvelder and McGehee, 2002; Picciotto, 2003; Dani and Bertrand, 2007), and in the striatum, where they are localized on dopaminergic terminals and control dopamine release (Tribollet et al., 2004; Quarta et al., 2007). In contrast, α_7 nACh receptors are present in both the VTA and the striatum but are localized on glutamatergic terminals, where they control glutamate release and, consequently, dopamine release (Fu et al., 2000; Kaiser and Wonnacott, 2000; Rassoulpour et al., 2005; Dani and Bertrand, 2006).

Pharmacological tools exist to dissect *in vivo* the role of α_7 and non-α_7 nACh receptors: methyllycaconitine (MLA) is a selective α_7 nACh receptor antagonist, whereas dihydrobetaerythroidine

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(DHBE) binds to β_2 subunits and is a selective antagonist for non-α_7 nACh receptors (Alkondon et al., 1992; Stauderman et al., 1998). With the use of these drugs, as well as the use of genetically engineered mice, it has been possible to dissect the role α_7 and non-α_7 nACh receptors play in the rewarding effects of nicotine (Picciotto, 2003). Although some contrasting reports exist (Markou and Paterson, 2001), it appears that the rewarding and psychotropic effects of nicotine are primarily mediated in the VTA (Corrigall et al., 1994; Ikemoto et al., 2006) by non-α_7 nACh receptors (Picciotto et al., 1998; Gommans et al., 2000; Grottick et al., 2000; Maskos et al., 2005; Walters et al., 2006).

In this study, we investigated whether selective nACh receptor antagonists were effective in diminishing the discriminative and reinforcing effects of cannabinoids and their ability to elevate dopamine levels in the shell of the nucleus accumbens (NAc).

Materials and Methods

Subjects. Adult male Sprague Dawley (Charles River, Wilmington, MA) and Long–Evans (Harlan Nossan, Milan, Italy) rats experimentally naive at the start of the study were housed individually in a temperature- and humidity-controlled room and maintained on a 12 h light/dark cycle. The lights were on a normal light cycle for the THC discrimination and *in vivo* microdialysis experiments but were on a reversed light cycle for the (*R*)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)methyl]pyrrolo-[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone, mesylate salt (WIN5,212-2) self-administration experiments. Different light/dark cycles were used to be consistent with our previous THC discrimination (Solinas et al., 2003), *in vivo* microdialysis (Solinas et al., 2006), and WIN 55,212-2 self-administration (Fattore et al., 2001) studies. All experiments were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Intramural Research Program, National Institute on Drug Abuse (NIDA) and European Commission regulations for animal use in research (86/609/EEC).

Drug-discrimination apparatus and procedure were the same as described previously (Solinas et al., 2003). Briefly, Sprague Dawley rats were trained under a discrete-trial schedule of food-pellet delivery to respond on one lever after an injection of a training dose of 3 mg/kg THC and on the other lever after an injection of 1 ml/kg of vehicle under a fixed-ratio 10 (FR10) schedule of food delivery with a 45 s timeout (TO). Injections of THC or vehicle were given intraperitoneally 30 min before the start of the 30 min session. Two measures were analyzed: (1) percentage of total lever presses made on the THC lever, which gives a quantitative indication of whether a drug produces discriminative effects similar to those induced by the training dose of THC (3 mg/kg); and (2) overall rate of lever-press responding, which gives an indication of any disruption of motor responses produced by the drug tested.

Intravenous self-administration apparatus and procedure were the same as described previously (Fattore et al., 2001). Briefly, under deep anesthesia, Long–Evans rats were surgically implanted with a catheter in the right jugular vein and left to recover for 6–7 d before starting self-administration training. Animals were trained to press a lever for a response-contingent infusion of WIN55,212-2 (12.5 and 25 μg/kg per injection) under a one-response (FR1) or five-response (FR5) fixed-ratio schedule of reinforcement during 2 h daily sessions. There was a 10 s TO after each injection. After stabilization of daily drug intake (no more than 15% variation over 3 d), rats received a saline injection (2 ml, i.p.) for habituation to future drug pretreatment, and self-administration training was then continued for an additional 4 d before testing with nicotinic compounds. Animals received one dose of each drug and a saline injection (5 ml/kg, i.p.), with a minimum of 5 d separating each treatment. The order of drug administration was varied between animals, and each treatment group included a minimum of six animals. During self-administration sessions, locomotor activity was monitored by photocells located 3.5 cm above the cage floor. Importantly, no alterations in locomotor activity were found after any of drug pretreatment compared with basal activity levels (mean of the last 3 d of training before testing) (Table 1).

Table 1. Locomotor activity during baseline and test self-administration sessions

Schedule	Dose of WIN	Baseline	MLA 1	MLA 3	MLA 5.6	DHBE 3	DHBE 5.6
FR1	12.5	258 ± 7		268 ± 14	244 ± 17	266 ± 13	252 ± 14
FR1	25	224 ± 8	248 ± 7	236 ± 12	268 ± 12		
FR5	12.5	268 ± 10		294 ± 8	260 ± 12	272 ± 9	

Data are expressed as mean ± SEM of locomotor counts. Doses for WIN55,212-2 (WIN) self-administration are expressed as micrograms per kilogram per injection, whereas doses for drug pretreatment are expressed as milligrams per kilogram, intraperitoneally.

Microdialysis apparatus and procedure were the same as described previously (Solinas et al., 2006). Briefly, under deep anesthesia, Sprague Dawley rats were surgically implanted with a concentric dialysis probe aimed at the shell of the NAc [anterior +2.0 and lateral 1.1 from bregma, vertical −7.9 from dura, according to the atlas by Paxinos and Watson (1998)] and left to recover for 24 h before microdialysis experiments. Ringer's solution (147.0 mM NaCl, 2.2 mM $CaCl_2$, 4.0 mM KCl) was delivered at a constant flow rate of 1 μl/min. Collection of dialysate samples (10 μl) started after 30 min, with samples collected every 10 min and immediately analyzed by an HPLC system coupled to electrochemical detection. Rats were treated only after stable dopamine values (<10% variability) were obtained for at least three consecutive samples. Each rat received one treatment only and was killed at the end of the experiment to allow brain removal for histological verification. Only rats with correct probe placement were included in the study (see supplemental Fig. 1, available at www.jneurosci.org as supplemental material, for probe placement).

Drugs. THC (RTI International, Research Triangle Park, NC), 50 mg/ml in ethanol, was dissolved in a 40% w/v solution of β-hydroxycyclodextrine (Sigma-RBI, St. Louis, MO). WIN55,212-2 (Tocris, Ellisville, MO) was first dissolved in one drop of Tween 80 and then diluted in saline solution. MLA (0.1–5.6 mg/kg) and DHBE (1–18 mg/kg) (Sigma-RBI, Trance, Italy) were dissolved in saline solution. MLA and DHBE were administered intraperitoneally 45 min before the start of the drug discrimination session (i.e., 15 min before THC injections) or 15 min before starting the self-administration session. The range of doses of cholinergic compounds used in this study was chosen based on existing literature on the *in vivo* effects of MLA and DHBE in studies measuring behavioral effects similar to those measured in this study (Gommans et al., 2000; Grottick et al., 2000; Markou and Paterson, 2001; Walters et al., 2006).

Data analysis. Discriminative-stimulus data were expressed as the percentage of the total responses on the two levers that were made on the THC-appropriate lever during the test session. Response-rate data were expressed as responses per second averaged over the session, with responding during TO periods not included in calculations. Data from sessions during which rats did not complete at least one fixed-ratio trial were excluded from analysis of drug-lever selection. For self-administration experiments, the cumulative number of responses on both the active and inactive levers over the 120 min was measured. For microdialysis experiments, basal dopamine values were calculated as the mean of three consecutive samples (differing no more than 10%) immediately preceding the first drug or vehicle injection, and results are expressed as a percentage of basal dopamine values. Statistical analysis was done using one-, two-, or three-way ANOVA, followed by Dunnet's, Bonferroni's, or Tukey's tests. A probability value of $p < 0.05$ was considered significant. For drug-discrimination experiments, data were also analyzed by nonlinear regression analysis using a sigmoidal dose–response (variable slope) equation. ED_{50} values were obtained for each compound; dose–response curves were considered significantly different when 95% confidence intervals of ED_{50} values did not overlap.

Results

Blockade of α_7, but not non-α_7, nACh receptors antagonizes the discriminative effects of THC

As shown in Figure 1*A* (top), rats perfectly discriminated the effects of 3 mg/kg THC (100% THC-lever selection) from those

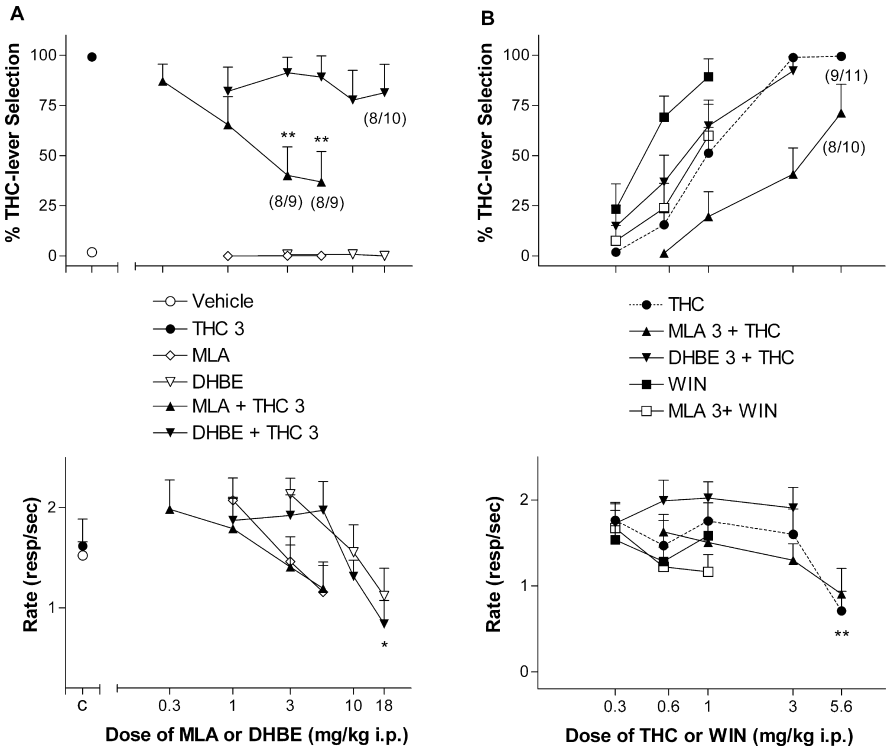

Figure 1. The α_7 nACh receptor antagonist MLA, but not the non-α_7 nACh receptor antagonist DHBE, significantly reduces the discriminative effects of THC and WIN55,212-2. ***A***, Effects of MLA and DHBE on discrimination of the 3 mg/kg training dose of THC (THC 3). C, Control value for vehicle alone. ***B***, Effects of selected doses of MLA (MLA 3) and DHBE (DHBE 3) on the dose–response curve for THC discrimination and WIN55,212-2 (WIN). Results represent the means ± SEM from 9–11 rats. $^{**}p < 0.01$ compared with 3 mg/kg THC (repeated-measures ANOVA, followed by *post hoc* Dunnett's test). Numbers in parentheses at higher doses indicate the number of rats that completed at least one fixed ratio during the session over the total number of rats in which the dose was tested. resp/sec, Responses per second.

of a vehicle injection (0% THC-lever selection). The selective α_7 antagonist MLA (0.3–5.6 mg/kg, i.p.) dose-dependently antagonized the discriminative effects of THC (one-way ANOVA, dose effect: $F_{(4,28)} = 6.12$; $p = 0.0011$) at doses that did not produce any THC-like discriminative effect by themselves (Fig. 1*A*, top) and did not significantly alter rates of responding (Fig. 1*A*, bottom). The 3 mg/kg dose of MLA (MLA 3) also produced a significant shift to the right in the dose–response curve for THC discrimination (ED_{50} for THC alone, 1.03; confidence intervals, 0.90–1.16; ED_{50} for MLA 3 plus THC, 3.23; confidence intervals, 1.50–4.97; two-way ANOVA, treatment effect: $F_{(1,8)} = 19.63$; $p = 0.0022$), as shown in Figure 1*B* (top). In contrast to results with MLA, the selective non-α_7 antagonist DHBE (1–18 mg/kg, i.p.) did not produce any THC-like discriminative effect, did not antagonize the discriminative effects of the 3 mg/kg training dose of THC (Fig. 1*A*, top), and did not produce any shift in the THC dose–response curve (Fig. 1*B*, top). However, the high dose of 18 mg/kg DHBE did significantly decrease rates of responding (Fig. 1*B*, bottom).

The synthetic cannabinoid CB1 agonist WIN55,212-2 (0.3–1 mg/kg, i.p.) generalized completely to the discriminative effects of THC, and MLA significantly antagonized these THC-like effects of WIN55,212-2 (ED_{50} for WIN55,212-2 alone, 0.46; confidence intervals, 0.35–0.57; ED_{50} for MLA 3 plus WIN55,212-2, 0.89; confidence intervals, 0.67–1.11; two-way ANOVA, treatment effect: $F_{(1,9)} = 6.47$; $p = 0.023$).

Blockade of α_7, but not of non-α_7, nACh receptors reduces self-administration of WIN55,212-2

In line with previous studies (Fattore et al., 2001), under a continuous (FR1) schedule of reinforcement, rats consistently self-administered intravenous injections of WIN55,212-2 at a dose of 12.5 μg/kg per injection with a mean of 21.08 ± 5.3 responses per session on the active lever, resulting in self-administration of a mean daily amount of 263.5 ± 66.25 μg/kg of WIN55,212-2 under basal conditions. As shown in Figure 2*A*, DHBE (3 and 5.6 mg/kg, i.p.) and the 3 mg/kg dose of MLA did not alter the mean total number of responses made on the active lever compared with baseline responding. In contrast, when rats were pretreated with 5.6 mg/kg MLA, self-administration responding significantly decreased to 7.33 ± 0.97 responses per session (−64.76%) (two-way ANOVA, treatment effect: $F_{(3,18)} = 4.51$; $p < 0.05$). When a higher dose (25 μg/kg per injection) of WIN55,212-2 was available for self-administration (Fig. 2*B*), responding stabilized at 16.77 ± 0.41 responses per session, resulting in self-administration of a mean daily amount of 419.25 ± 24.25 μg/kg of the cannabinoid. As shown in Figure 2*B*, administration of 1 and 3 mg/kg doses of MLA did not significantly affect responding, whereas the higher 5.6 mg/kg dose of MLA drastically reduced active lever pressing to 4.17 ± 0.52 responses per session (−74.32%). Two-way ANOVA showed a significant effect of treatment ($F_{(2,12)} = 3.53$; $p < 0.05$).

When the response requirement per injection was increased from one to five responses (FR5) at a dose of 12.5 μg/kg per injection of WIN55,212-2, rats increased their responding to a mean of 98.17 ± 4.36 responses per session, resulting in a daily mean number of 19.63 ± 0.87 injections per session (Fig. 2*C*). Under these conditions, MLA at the dose of 5.6 mg/kg, but not at the lower dose of 3 mg/kg, significantly decreased (−66.72%) cannabinoid self-administration responding to 32.17 ± 4.85 responses per session ($F_{(2,12)} = 2.11$; $p < 0.05$), whereas DHBE (5.6 mg/kg) had no significant effect.

Blockade of α_7, but not of non-α_7, nACh receptors reduces THC-induced elevations in dopamine levels in the NAc shell

Systemic injections of 3 mg/kg THC increased extracellular levels of dopamine in the NAc shell by ~60% compared with basal levels (treatment effect: $F_{(1,29)} = 7.89$; $p < 0.01$), as shown in Figure 3, *A* and *C*. Administration of 3 and 5.6 mg/kg intraperitoneal doses of MLA, that by themselves did not alter dopamine levels (Fig. 3*B*), completely blocked THC-induced elevations in dopamine levels (Fig. 3*A*) (pretreatment effect: $F_{(2,29)} = 3.68$, $p < 0.05$; pretreatment × time interaction: $F_{(24,348)} = 1.89$, $p < 0.01$). In contrast, DHBE (3 and 5.6 mg/kg, i.p.) did not alter dopamine levels by itself (Fig. 3*D*) and did not alter THC-induced elevations in dopamine levels (Fig. 3*C*).

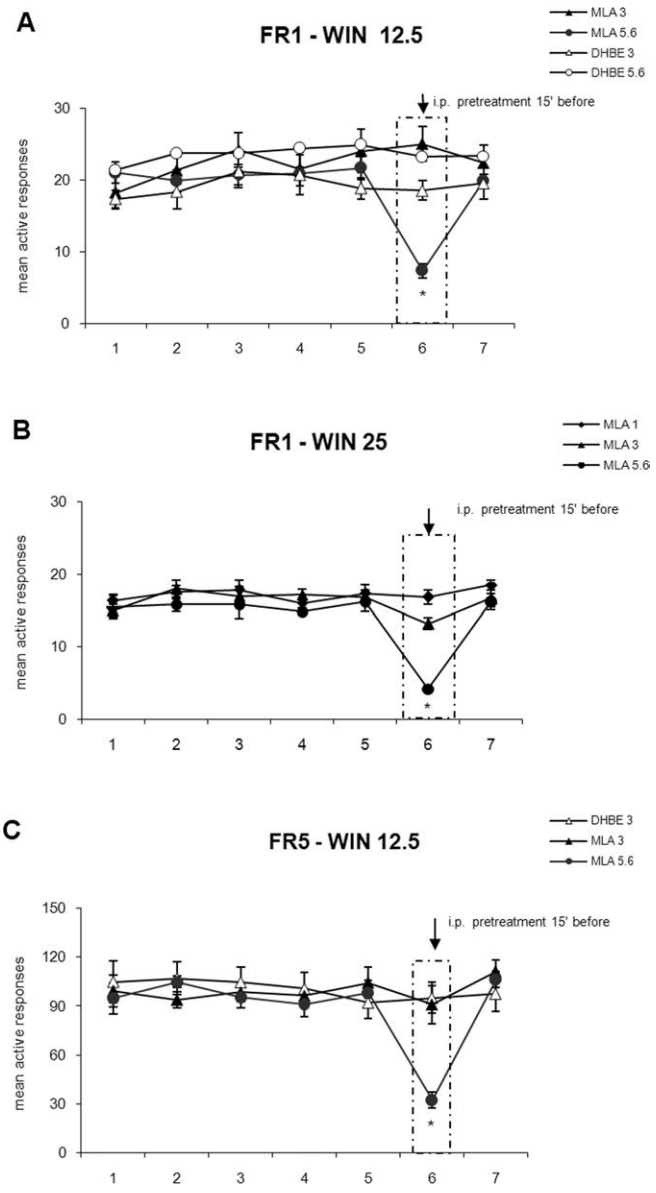

Figure 2. MLA, but not DHBE, significantly reduces the self-administration of WIN55,212-2. ***A***, ***B***, Effects of MLA and DHBE on WIN55,212-2 self-administration under an FR1 schedule at the doses of 12.5 μg/kg (WIN 12.5) and 25 μg/kg (WIN 25) per injection. ***C***, Effects of MLA and DHBE on WIN55,212-2 (12.5 μg/kg per injection) self-administration under an FR5 schedule of reinforcement. Results represent the means ± SEM from six rats. *$p < 0.05$ compared with previous baseline (two-way ANOVA, followed by Bonferroni's *post hoc* test). MLA 1, MLA 3, and MLA 5.6 correspond to doses of 1, 3, and 5.6 mg/kg MLA, respectively. DHBE 3 and DHBE 5.6 correspond to doses of 3 and 5.6 mg/kg DHBE, respectively.

Discussion

In this study, we demonstrated that α_7 nACh receptor blockade can reverse the discriminative effects of THC and WIN55,212-2, reduce the self-administration of WIN55,212-2, and block the ability of THC to increase dopamine levels in the NAc shell, an effect generally considered fundamental to reinforcement of drug-taking habits (Di Chiara, 2002). These effects appear selective for α_7 nACh receptors, because the non-α_7 nACh receptor antagonist DHBE did not alter any of the cannabinoid-induced behavioral or neurochemical effects. Together, our results indicate that drugs blocking α_7 nACh receptors may be promising as new therapeutic tools for the treatment of cannabis abuse and addiction.

Previous studies investigating interactions between cannabinoid and ACh systems on behavior have focused on cognitive-impairing effects of THC (Lichtman et al., 2002). The present results demonstrate that the ACh system, possibly through interactions with dopaminergic systems (Mansvelder and McGehee, 2002; Picciotto, 2003; Dani and Bertrand, 2007), also plays an important role in the abuse-related behavioral and neurochemical effects of cannabinoids. These results are consistent with our recent findings that discrimination of THC is facilitated by administration of nicotine (Solinas et al., 2007).

Cholinergic and cannabinoid systems seem to strongly interact with each other. Localizations of nicotinic and cannabinoid receptors often overlap, and cannabinoid CB1 receptors negatively control release of ACh (Schlicker and Kathmann, 2001). On the other hand, activation of nicotinic receptors leads to increased intracellular levels of calcium (Dani et al., 2001), which is known to stimulate release of endogenous cannabinoids such as anandamide (Piomelli, 2003). Although it is controversial whether cannabinoid CB1 agonists decrease or increase ACh neurotransmission *in vivo* (Gessa et al., 1997; Tzavara et al., 2003; Pisanu et al., 2006), findings from several studies indicate that their behavioral effects are positively modulated by ACh agonists (Pertwee and Ross, 1991; Valjent et al., 2002; Solinas et al., 2007).

In the present study, MLA was effective at a 3 mg/kg dose in the discrimination and dialysis experiments, but only at a higher 5.6 mg/kg dose in the self-administration experiment. The use of WIN55,212-2, rather than THC, does not explain this effect, because WIN55,212-2 produces THC-like effects in rats discriminating THC from vehicle that are antagonized by 3 mg/kg MLA. One possible reason for needing a higher dose of MLA in the self-administration experiment is that the half-life of MLA is relatively short [only 37 min in rats after intraperitoneal administration (Turek et al., 1995)] and higher doses of MLA would be needed to block α_7 receptors for the entire duration of 120 min self-administration sessions than for 30 min discrimination sessions. This possibility is supported by the finding that when MLA was administered 120 min before a discrimination session, the dose of 5.6 but not 3 mg/kg MLA reversed the discriminative effects of THC (supplemental Fig. 2, available at www.jneurosci.org as supplemental material). Another possible reason for discrepancies in dose between experiments is that differences in sensitivity to the effects of MLA may exist between Sprague Dawley and Long–Evans rats.

Interestingly, doses of MLA that were effective in reducing the discriminative effects of THC or reducing WIN55,212-2 self-administration responding in the present experiments are ineffective in blocking similar effects of nicotine, whereas doses of DHBE that did not alter the behavioral effects of THC or WIN55,212-2 in the present experiments are effective in blocking similar behavioral effects of nicotine (Gommans et al., 2000; Grottick et al., 2000; Walters et al., 2006) (but see Markou and Paterson, 2001) (supplemental Fig. 3, available at www.jneurosci.org as supplemental material). Thus, the roles α_7 and non-α_7 ACh receptors play in modulating the discriminative and reward-related behavioral effects of cannabinoid CB1 agonists and nicotine may differ substantially.

Because α_7 nACh receptors are believed to be involved in cognitive functions (Levin et al., 2006), it could be argued that reduction by MLA of THC discrimination was, at least in part, attributable to memory impairment. However, if this were true, MLA should have similarly affected discrimination of vehicle and all doses of THC, leading to ~50% (chance level) THC-lever selection. In contrast, 3 mg/kg MLA produced a parallel shift of

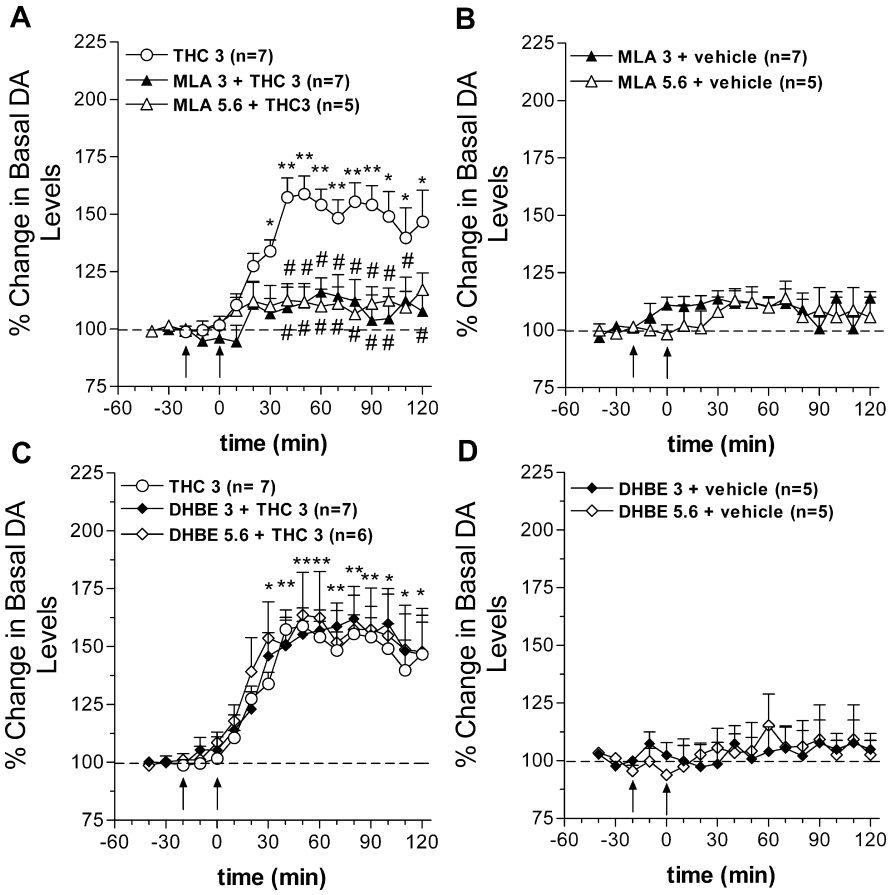

Figure 3. MLA, but not DHBE, significantly antagonizes the THC-induced elevations of dopamine (DA) levels in the shell of the NAc. Effects of MLA (***A***) and DHBE (***B***) on THC-induced elevations in dopamine levels (***A***, ***C***) and on basal dopamine levels (***B***, ***D***). Results represent means ± SEM from five to seven rats. $^{*}p < 0.05$, $^{**}p < 0.01$ compared with baseline; $^{\#}p < 0.05$ compared with the corresponding time point of 3 mg/kg THC (THC 3) alone (two-way ANOVA, followed by Tukey's *post hoc* test). MLA 3 and MLA 5.6 correspond to doses of 3 and 5.6 mg/kg MLA, respectively. DHBE 3 and DHBE 5.6 correspond to doses of 3 and 5.6 mg/kg DHBE, respectively.

the dose–response curve for THC discrimination. In addition, whereas the cognitive effects of intra-brain injections of MLA have been clearly demonstrated (Levin et al., 2006), systemic injections of MLA produce very limited alterations in memory, and only at doses of MLA higher than those used in our study (Blondel et al., 2000; Davis and Gould, 2006). Finally, in the WIN55,212-2 self-administration experiments, there was a profound decrease in responding on the active lever but no change in responding on the inactive lever after MLA administration (data not shown), again suggesting that the effects of MLA were selective for the discriminative and reinforcing effects of cannabinoids and were not caused by nonspecific effects on cognition or activity.

Systemic administration of MLA significantly reduced not only the discriminative effects of THC and WIN55,212-2 and the self-administration of WIN55,212-2, but also the ability of THC to increase dopamine levels in the NAc shell, an effect considered central for the reinforcing effects of many abused drugs, including THC (Tanda et al., 1997; Tanda and Goldberg, 2003). Two recent studies (Fadda et al., 2006; Lecca et al., 2006) demonstrated that dopamine levels in the shell, but not in the core, of the NAc are elevated by self-administered WIN55,212-2, supporting the involvement of dopamine mesolimbic neurotransmission in the reinforcing effects of cannabinoids. Consistent with these observations and the central role of dopamine in abuse-related effects of cannabinoids, the significant reductions in THC and WIN55,212-2 discrimination and the reduction in WIN55,212-2 self-administration produced by MLA were paralleled by the blockade of THC-induced elevations in dopamine levels in the shell of the NAc produced by MLA.

In conclusion, our results demonstrate that blockade of α_7 nACh receptors can reduce behavioral and neurochemical effects of THC that are related to its abuse. Importantly, MLA produced its effects at doses that did not produce depressant or toxic effects, pointing to drugs that block α_7 nACh receptors as useful agents in the treatment of cannabis abuse in humans.

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