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PREFRONTAL CORTICAL MODULATION OF ACETYLCHOLINE RELEASE IN POSTERIOR PARIETAL CORTEX

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Abstract—Attentional processing is a crucial early stage in cognition and is subject to "top-down" regulation by prefrontal cortex (PFC). Top-down regulation involves modification of input processing in cortical and subcortical areas, including the posterior parietal cortex (PPC). Cortical cholinergic inputs, originating from the basal forebrain cholinergic system, have been demonstrated to mediate important aspects of attentional processing. The present study investigated the ability of cholinergic and glutamatergic transmission within PFC to regulate acetylcholine (ACh) release in PPC. The first set of experiments demonstrated increases in ACh efflux in PPC following AMPA administration into the PFC. These increases were antagonized by co-administration of the AMPA receptor antagonist DNQX into the PFC. The second set of experiments demonstrated that administration of carbachol, but not nicotine, into the PFC also increased ACh efflux in PPC. The effects of carbachol were attenuated by co-administration (into PFC) of a muscarinic antagonist (atropine) and partially attenuated by the nicotine antagonist mecamylamine and DNQX. Perfusion of carbachol, nicotine, or AMPA into the PPC did not affect PFC ACh efflux, suggesting that these cortical interactions are not bi-directional. These studies demonstrate the capacity of the PFC to regulate ACh release in the PPC via glutamatergic and cholinergic prefrontal mechanisms. Prefrontal regulation of ACh release elsewhere in the cortex is hypothesized to contribute to the cognitive optimization of input processing. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: attention, basal forebrain, cortex, microdialysis, glutamate.

Attention describes a complex set of operations involved in the detection, selection and discrimination of stimuli and the allocation of processing resources to competing attentional demands. The efficacy of attentional processing contributes to the efficiency of higher order cognitive processes, such as certain forms of learning and memory recall (Sarter et al., 2003, 2005). As such, significant cognitive dysfunctions may arise from the inability to process appropriately and effectively relevant stimuli and to allocate adequate processing resources (Sarter, 1994; Everitt and Robbins, 1997; Sarter and Bruno, 1999). Studies using laboratory animals revealed the importance of the basal forebrain cortical cholinergic system (BFCS) for attentional processing. Damage to the basal forebrain or depletions of acetylcholine (ACh) in cortex results in marked performance deficits in tasks explicitly designed to tax attentional processing (McGaughy and Sarter, 1998; McGaughy et al., 1996, 2002; Turchi and Sarter, 1997). Moreover, performance in such tasks is sufficient to stimulate cortical ACh release (Arnold et al., 2002; Himmelheber et al., 2000; Dalley et al., 2001; Passetti et al., 2000). Finally, a growing body of evidence indicates that cholinergic mechanisms contribute to attentional processing in humans as well (Foulds et al., 1996; Kumari et al., 2003; Wilens et al., 1999).

Attention is modified by knowledge-driven, practice-based, or goal-oriented information. This modulation, referred to as top-down regulation (see Desimone and Duncan, 1995), can enhance the processing of relevant sensory input, bias the subjects toward spatial locations associated with sensory stimuli, and suppress the processing of irrelevant information (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002). Although neurophysiological and human functional imaging studies have demonstrated top-down regulation in several brain systems (Desimone and Duncan, 1995; Shulman et al., 1997; Hopfinger et al., 2000; Kastner and Ungerleider, 2000), the specific neuronal mechanisms that mediate this aspect of cognitive regulation remain poorly understood.

It is hypothesized that a distributed neural network underlies attentional processing (Mesulam, 1981, 1990), and that multiple aspects of this network contribute to top-down regulation (Sarter et al., 2001). Extensive evidence suggests that top-down regulation is a component of frontal cortical regulation of executive functions, and mediated via the prefrontal recruitment of sensory and sensory associational cortical areas, including the posterior parietal cortex (PPC; for reviews see Coull, 1998; Cabeza and Nyberg, 2000). Several potential cortical and sub-cortical mechanisms could contribute to this type of regulation. We have hypothesized that the BFCS, consisting of cholinergic efferents projecting to all areas and layers of the cortex (Woolf, 1991), and receiving afferent input from the prefrontal cortex (PFC; Zaborszky et al., 1997) represents a component of the PFC efferent network that mediates

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Abbreviations: ACh, acetylcholine; aCSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methylisoxadole-4-propionic acid; ANOVA, analysis of variance; BFCS, basal forebrain cortical cholinergic system; DNQX, 6,7-dinitroquinoxaline-2,3-dione; PFC, prefrontal cortex; PPC, posterior parietal cortex.

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top-down effects (Sarter et al., 2001, 2005). The PFC control of posterior cortical information processing could potentially occur via direct cortico-cortical interactions and/or via corticofugal loops, including transmission through the BFCS.

The present experiments were designed to investigate glutamatergic and cholinergic mechanisms of PFC regulation of ACh release in PPC utilizing dual probe *in vivo* microdialysis, to begin to elucidate potential mechanisms of the PFC regulation and recruitment of cortical cholinergic transmission in posterior sensory and sensory associational areas. The results indicate that the PFC regulates posterior cortical ACh release, via cholinergic and glutamatergic transmission, and that this regulation is unidirectional within cortex.

EXPERIMENTAL PROCEDURES

Subjects and habituation

Young adult male Fisher 344/Brown Norway F1 hybrid rats (250–400 g) were used for all experiments (total $n=37$). Animals were individually housed in a temperature- (23 °C) and humidity- (45%) controlled environment on a 12-h light/dark cycle (lights on 06:30 h) with food and water available *ad libitum*. All housing, surgery, experimentation, and euthanasia procedures were approved by the Ohio State University Animal Care and Use Committee, and were performed in AAALAC approved facilities. These experiments conformed to guidelines on the ethical use of animals. Every attempt was used to minimize the number of animals used and their suffering.

Three to 4 days prior to surgery, animals were handled and habituated to the microdialysis testing environment, consisting of a clear, plastic bowl (35 cm height×38 cm diameter; CMA, Stockholm, Sweden) lined with corncob bedding, in a separate testing room. Animals were placed in the test bowls at the beginning of each day and returned to their homecages prior to the onset of the dark cycle (18:30 h).

Stereotaxic surgery

On the morning following the habituation period, animals were anesthetized with isoflurane gas, using a SurgiVet machine (Anesco/SurgiVet, Waukesha, WI, USA). Gas was carried via oxygen, with delivery rate of 2.0% isoflurane and a flow rate of 0.6 ml/min.

Animals were then implanted with microdialysis guide cannula (0.38 mm o.d.; SciPro, Inc., North Tonawanda, NY, USA) into the PPC (from bregma in mm using the atlas of Paxinos and Watson [1986]: AP −4.4, ML 2.5, DV 0.5 at a 50° side angle) and the ipsilateral mPFC (from bregma in mm: AP 2.7, ML 0.8, DV 1.0; Fig. 1). Hemispheres were counterbalanced in all studies. Cannula were fixed with stainless steel screws and dental cement. At the conclusion of surgery, animals were given a prophylactic dose of amoxicillin antibiotic (100 mg/kg s.c.). Animals were then returned to their homecages and allowed a recovery period of 3 days prior to testing. Animals were habituated to the testing environment each day of the recovery period.

General microdialysis procedure

For all experiments, each animal received a total of four microdialysis sessions, in counterbalanced order. This microdialysis procedure allows each animal to serve as its own control and also permits the conduct of dose-response studies or agonist/antagonist studies within the same subject. It has been validated for cortical (Nelson et al., 2002; Moore et al., 1995) and striatal (Johnson and Bruno, 1995) ACh efflux by the absence of significant session effects on basal or stimulated ACh efflux.

On a microdialysis testing day, animals were placed in the test environment at least 30 min prior to insertion of probes (between 08:00 and 10:00 h). The stainless steel dummy stylets were removed from the cannula, and concentric microdialysis probes (SciPro Inc.; 3.0 mm active membrane, 0.2 mm o.d.) were inserted into each guide cannula. A medium of artificial cerebrospinal fluid (aCSF) containing, in mM: NaCl 166.5, $NaHCO_3$ 27.5, KCl 2.4, $CaCl_2$ 1.2, Na_2SO_4 0.5, KH_2PO_4 0.5, glucose 1.0, pH 6.9, was perfused through each probe at a rate of 1.25 μl/min. No acetylcholinesterase inhibitor was utilized in the perfusion medium for any experiment. Following probe insertion, a 3 h washout period was observed to ensure that ACh efflux in the probe diffusion zone maximally reflected impulse-dependent release of ACh (Moore et al., 1992). Following this period, collections began at 15 min intervals, beginning with four baseline collections. Following the baseline period, the line leading to the PFC probe (or the PPC probe in the case of the PPC drug experiment) was switched from a syringe containing aCSF alone to a syringe containing aCSF+drug (in the case of a vehicle session, the line from the syringe containing aCSF alone was removed and then replaced). Following a 15 min interval to allow drug to fully perfuse through the probe, 90 min of subsequent drug collections (six) were taken while drug was perfused. In the case of antagonist co-perfusion studies, 30 min of initial drug collections were taken while the antagonist alone was perfused, followed by a switch to a line containing the antagonist+agonist, and then 75 min of collections were taken while both drugs were perfused. Following the final drug perfusion period, the line to the probe was switched back to a line containing aCSF alone and a 60 min (45 min for antagonist co-perfusion studies) post-drug collection period was conducted. Following the completion of the last collection, probes were removed, dummy stylets were replaced in the guides, and animals were returned to their home cages. Post-microdialysis recoveries were measured using a solution containing a known concentration of ACh. Recovery was reliably demonstrated to be approximately 11±4%. ACh values were not corrected for recovery.

Microdialysis procedure for the effects of reverse dialysis of glutamatergic ligands

For each of the two agonist experiments, following the establishment of the baseline period (four collections), the swivel to the PFC probe was switched from aCSF and either reconnected to aCSF alone, or connected to a syringe containing aCSF+NMDA (100, 250, 500 μM) or AMPA (5, 25, 50 μM), depending on the experiment. These concentrations of NMDA and AMPA were chosen based on pilot studies, and also on data from previous microdialysis studies (Kretschmer et al., 2000; Zapata et al., 2000; Del Arco and Mora, 2002; Lorrain et al., 2003). This concentration range is also safely below those producing excitotoxicity using microdialysis (Page et al., 1993; Weiss et al., 1994; Vanicky et al., 1998). Dose-response studies for each class of agonist were conducted within the same group of subjects.

For the AMPA/antagonist experiment, the baseline period was established as described earlier (four collections). At the conclusion of the baseline period, the line to the PFC probe was switched from aCSF alone and either replaced with aCSF alone (vehicle) or switched to a syringe containing one of the antagonist treatments (100 μM atropine [muscarinic], 100 μM mecamylamine [nicotinic], 100 μM DNQX [AMPA receptor antagonist]). The concentrations were chosen based on pilot studies, and data from other microdialysis studies (Nisell et al., 1994; Moore et al., 1996; Marshall et al., 1997; Moor et al., 1998; Reid et al., 1999; Del Arco and Mora, 2002). The ability of various classes of antagonists to attenuate the AMPA effect was studied in the same group of animals.

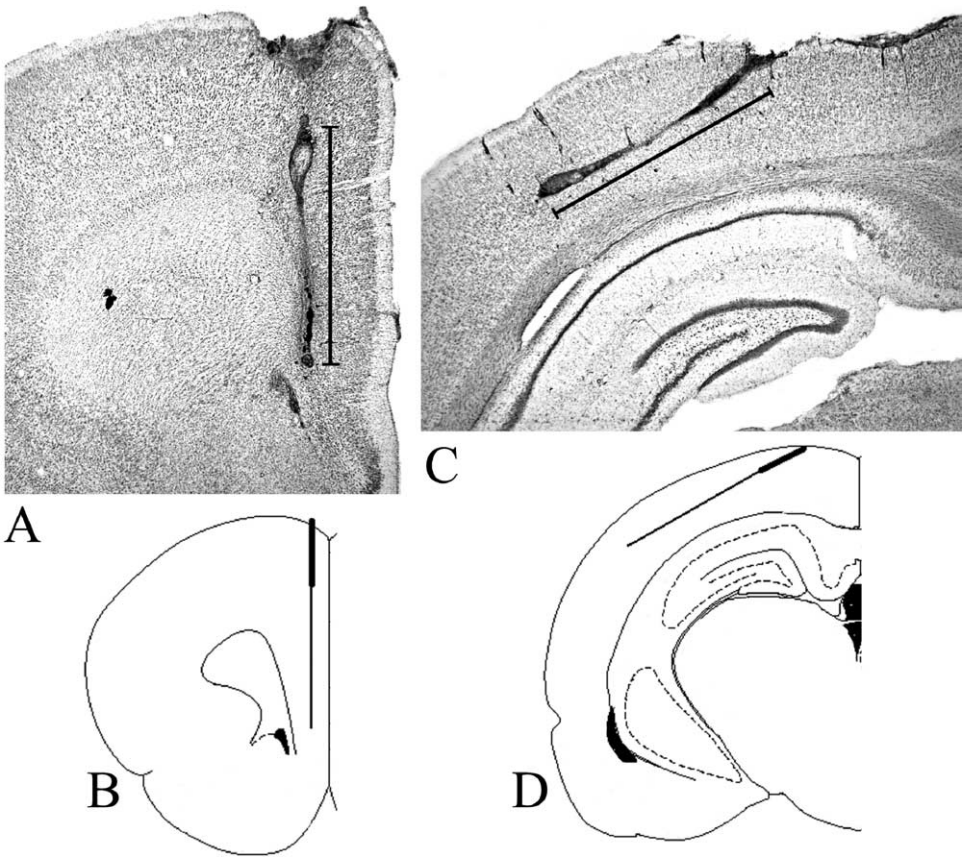

Fig. 1. Coronal sections showing representative placements of the microdialysis probes (length of active membrane is 3.0 mm) in the medial prefrontal (A) and the posterior parietal (C) cortex (the bars in A and C are 3.0 mm long and were placed next to the probe sites). The probes placed in the medial PFC (B) penetrated the ventral third of the cingulated cortex and the entire prelimbic and infralimbic cortex. In the posterior parietal lobe, probes were placed in Krieg's area 7 (Krieg, 1946; see also Fig. 1 in Kolb et al., 1994).

Microdialysis procedure for the reverse dialysis of cholinergic ligands

For each of the two agonist experiments, following the establishment of the baseline period (four collections), the swivel to the PFC probe was disconnected from aCSF and either reconnected to aCSF alone, or connected to a line containing aCSF+carbachol (100, 250, 500 μM) or nicotine (1, 5, 10 mM), depending on the experiment. The concentrations of carbachol and nicotine chosen were based on extensive pilot studies, and also on concentrations from previous microdialysis studies (Moor et al., 1995; Van Gaalen et al., 1997; Gray and Connick, 1998; Reid et al., 1999; Gioanni et al., 1999).

For the carbachol/antagonist experiment, the baseline period was established as described earlier (four collections). At the conclusion of the baseline period, the line to the PFC probe was switched from aCSF alone to either aCSF alone (vehicle) or switched to one of the antagonist treatments (100 μM atropine [muscarinic], 100 μM mecamylamine [nicotinic], 100 μM DNQX [AMPA receptor antagonist]). The antagonist was allowed to perfuse for 15 min, followed by 30 min of collections (two) with the antagonist alone. At the conclusion of this period, the line to the PFC probe was switched from antagonist to the antagonist (or vehicle)+500 μM carbachol, the maximum dose from the agonist experiment demonstrating increases in ACh efflux in both the PFC and the PPC.

Quantification of ACh

Dialysate samples were stored at −80 °C prior to analysis. Samples were analyzed with high performance liquid chromatography with electrochemical detection. A volume of 15.0 μl was injected by autosampler (ESA Inc., Chelmsford, MA, USA) and ACh and choline were separated by a C-18 carbon polymer column (ESA Inc.; 250×3 mm) using a sodium phosphate mobile phase (in mM: Na_2HPO_4 100.0, TMACl 0.5, 1-octanesulfonic acid 2.0, 0.005% microbicide reagent MB, pH=8.0; flow rate of 0.5 ml/min). A pre-column immobilized enzyme reactor (ESA Inc.) was utilized to hydrolyze choline in order to reliably detect baseline-to-baseline ACh peaks in the absence of an acetylcholinesterase inhibitor. This procedure reduced interference from the large choline peak and allowed the detector to be set at maximal gain in order to optimize signal:noise ratios. ACh and choline were hydrolyzed post-column by an additional enzyme reactor (ESA Inc.), converted to H_2O_2 (Potter et al., 1983), and measured using a "peroxidase-wired" (Huang et al., 1995) ceramic glassy carbon electrode, held at an applied potential of −200 mV. The detection limit under these conditions was approximately 2.0 fmol/15 μl injection.

Histology

Following the completion of the final session, animals were anesthetized with an overdose of Nembutal and then transcardially perfused with 0.9% heparinized saline followed by 10.0% formalin. Brains were then removed and stored in formalin for at least 24 h. Brains were then transferred to a 30% sucrose phosphate buffer solution where they were allowed to sink. Sections (50 μm thick) were then taken through PFC and PPC with a cryostat, mounted on slides, and Nissl-stained with

Cresyl Violet to verify probe placements. Animals with placements outside the PFC or the PPC were discarded from subsequent analysis.

Data analysis

For each experiment, changes in absolute basal ACh efflux across sessions and treatments over time were analyzed using two-way repeated measures analyses of variance (ANOVAs). In the absence of significant effects of session or treatment, basal efflux was then defined as the mean of the baseline period, and subsequent data expressed as percentage change from the mean baseline value. Statistical analyses of drug effects were conducted using an overall within-subject ANOVA, with DOSE or DRUG and TIME as within-subjects variables. TIME was defined as the last baseline collection and all drug perfusion time-points. For the antagonist co-administration studies, TIME included the final baseline collection and all drug co-administration timepoints. Two-way ANOVAs were then utilized to test differences between specific treatment conditions where appropriate. One-way ANOVAs were also utilized to determine the time that post-drug ACh efflux levels returned to basal levels. Significance was defined as $P<0.05$, and the Huynh-Feldt correction was utilized to reduce type I errors associated with repeated measures ANOVAs (Vasey and Thayer, 1987). All statistical tests were performed using SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Histological analysis

Fig. 1 shows representative placements in the PFC and PPC (see legend for details). Any subjects that had either probe located outside the region of interest were excluded from subsequent analysis.

Effects of AMPA administration within PFC on ACh efflux in PPC

Basal ACh efflux. In animals receiving AMPA perfusions into the PFC ($n=7$), basal efflux of ACh in PPC was consistent across the various treatment conditions. As in our previous studies, basal ACh levels did not differ across the four microdialysis sessions ($P>0.05$) nor across the four doses of AMPA administered ($P>0.05$). Basal ACh release (fmol/15 μl sample) in the PPC for each of the four conditions was vehicle: 15.3±5.7; 5 μM AMPA: 10.8±2.9; 25 μM AMPA: 15.0±6.4; 50 μM AMPA: 15.8±4.9. Therefore, subsequent analyses were conducted on data expressed as percent change from mean baseline as shown in Fig. 2.

AMPA-stimulated ACh efflux. The effects of AMPA perfusions into PFC on ACh efflux in PPC are shown in Fig. 2. Intra-PFC AMPA dose-dependently increased ACh efflux in PPC (DOSE [$F_{3,18}=5.637$, $P=0.011$]; TIME [$F_{6,36}=9.713$, $P<0.001$]; DOSE×TIME [$F_{18,108}=3.291$, $P<0.001$]). Subsequent multiple comparisons demonstrated that the highest dose of AMPA (50 μM) produced a significantly higher efflux of ACh in the PPC than both the vehicle ([$F_{1,6}=10.476$, $P=0.018$] and the lowest dose (5 μM; [$F_{1,6}=8.979$, $P=0.024$]). The intermediate dose (25 μM) increased ACh efflux over vehicle (DOSE×TIME:

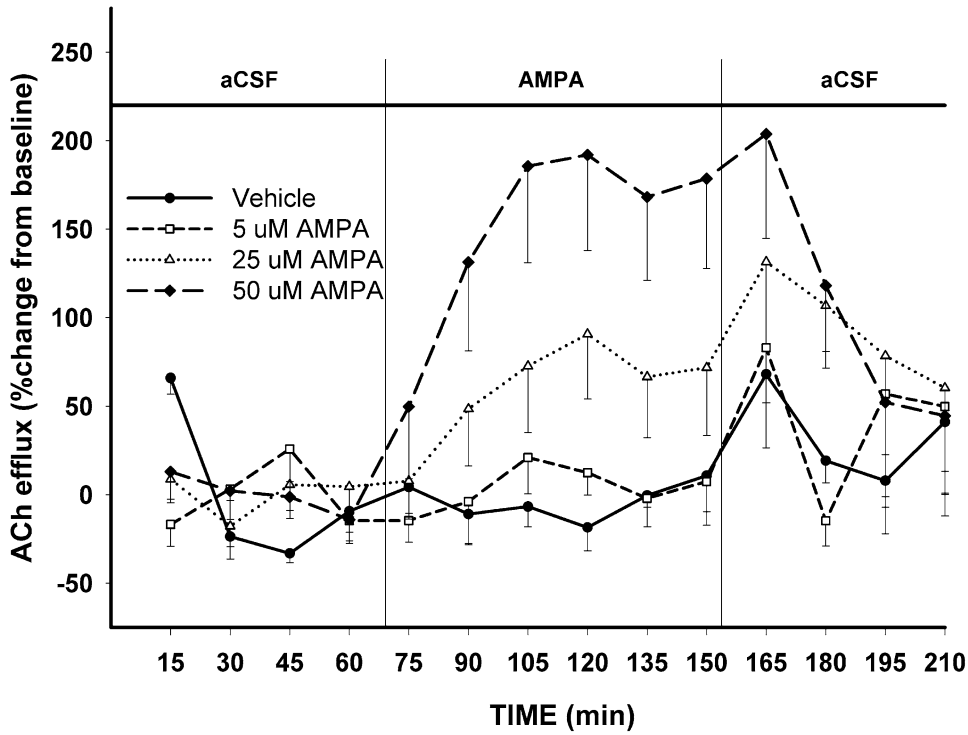

Fig. 2. Mean (±S.E.M.) ACh efflux (% change from mean baseline) in the PPC of animals ($n=7$) receiving AMPA. All animals received all treatments in counterbalanced order. Following baseline collections (0–60 min), AMPA was administered in the PFC via reverse dialysis, and 90 min of drug perfusion collections were taken. Drug was then removed from the PFC, and 60 min of post-drug collections were taken. As shown, intra-PFC AMPA dose-dependently increased ACh efflux in the PPC.

[$F_{6,36}$=5.053, P=0.002]). The lowest dose (5 μM) did not significantly increase ACh efflux over vehicle (Ps>0.05). ACh efflux did not significantly differ from baseline across the doses 30 min (i.e. 180 min collection point) following the removal of the drug (DOSE: [$F_{3,18}$=0.163, P=0.920], DOSE×TIME: [$F_{6,36}$=0.181, P=0.980]). In contrast to these large changes in distal ACh efflux, the perfusion of AMPA had no effect locally within the PFC (all Ps>0.05; data not shown). Moreover, unlike the case with AMPA, administration of NMDA (100, 250, 500 μM) into the PFC did not significantly affect ACh efflux in the PPC (all Ps>0.05; data not shown).

Effects of AMPA/antagonist co-administration on PPC ACh efflux

Basal ACh efflux. Basal ACh efflux in PPC in these animals (n=5) did not differ across sessions or doses (all Ps>0.05). Basal ACh release (fmol/15 μl sample) for each treatment condition were vehicle+50 μM AMPA: 11.3±2.6; 100 μM atropine+50 μM AMPA: 11.0±2.3; 100 μM mecamylamine+50 μM AMPA: 13.3±3.6; 100 μM DNQX+50 μM AMPA: 15.8±8.8.

ACh efflux following AMPA/antagonist co-administration. The effects of AMPA co-administered with vehicle or an antagonist into the PFC on PPC ACh efflux are shown in Fig. 3. Administration of the antagonists alone following the baseline period did not significantly affect ACh efflux compared with basal levels (all Ps>0.05). An overall ANOVA on the effects of all antagonist conditions did not reveal a significant alteration of the effects of AMPA on PPC ACh efflux. However, Fig. 3 indicates that DNQX administration almost completely blocked the effects of AMPA on PPC ACh efflux, and this finding was substantiated by an analysis that was restricted to the effects of the AMPA antagonist DNQX as compared with the vehicle condition (DRUG: [$F_{1,4}$=10.524, P=0.032]. ACh efflux did not differ from basal efflux following the removal of the drug (all Ps>0.05). These data indicate that co-administration of DNQX, but not cholinergic antagonists, with AMPA into the PFC attenuates the distal effects of AMPA alone on ACh efflux in PPC.

Effects of intra-PFC carbachol administration on PPC ACh efflux

Basal ACh efflux. Basal ACh efflux in PPC (n=6) did not vary across doses administered (all Ps>0.05). However, basal ACh efflux varied across sessions ([$F_{3,15}$=4.896, P=0.014]). The mean baseline values (fmol/15 μl sample) for each session were session 1: 18.1±3.9; session 2: 6.9±1.2; session 3: 12.3±3.4; session 4: 10.0±2.1. Post hoc analysis indicated that ACh efflux was higher in session 1 when compared with session 2 [$F_{1,5}$=9.293, P=0.028]. None of the other sessions were significantly

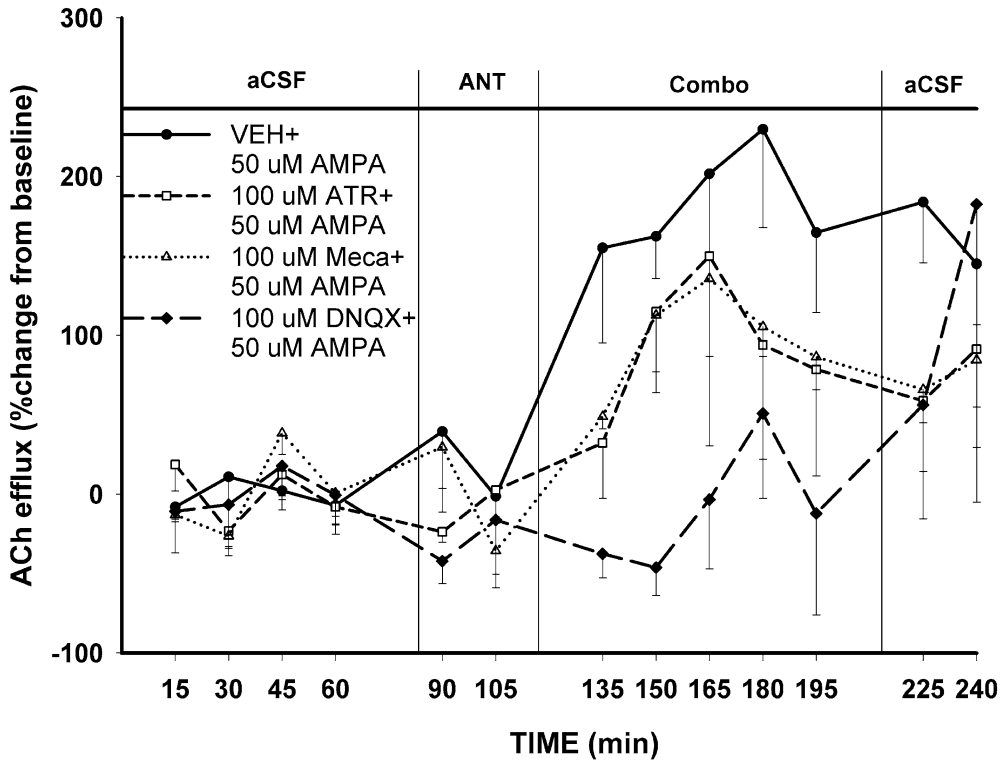

Fig. 3. Mean (±S.E.M.) ACh efflux in the PPC of animals (n=5) receiving co-administration of an antagonist [vehicle (VEH), atropine, mecamylamine, DNQX] and 50 μM AMPA into the PFC. All animals received all treatments in counterbalanced order. Following baseline collections (0–60 min), VEH or antagonist was administered to the PFC for 30 min. This was followed by co-administration of the antagonist (or VEH)+AMPA. Following the drug perfusion period, aCSF was then perfused for 45 min at the conclusion of the testing period. DNQX (diamonds) significantly attenuated the AMPA-induced ACh efflux in the PPC. The cholinergic antagonists produced a moderate, non-significant attenuation in the AMPA-induced ACh efflux.

different from each other, and as all doses of drug were counterbalanced across animals, it is unlikely that basal differences among sessions contributed to any significant and systematic drug effects in this experiment. Therefore, subsequent analyses were conducted on data expressed as percent change from mean baseline as shown in Fig. 4 (top panel). Basal ACh release (fmol/15 μl sample) in the PPC for each drug condition was vehicle: 13.5±3.0; 100 μM carbachol: 13.4±4.3; 250 μM carbachol: 11.8±3.7; 500 μM carbachol: 8.6±1.6.

Carbachol-stimulated ACh efflux. The effects of carbachol perfusion in the PFC on ACh efflux in the PPC are shown in Fig. 4 (top panel). Carbachol dose-dependently increased ACh efflux (DOSE [$F_{3,15}$=16.807, P<0.001]; TIME [$F_{6,30}$=9.342, P<0.001]; DOSE×TIME [$F_{18,90}$=3.853, P<0.001]). Subsequent comparisons of individual doses reveal that the two highest doses of carbachol (250 and 500 μM) significantly increased ACh efflux compared with the effects of both vehicle (250 μM DOSE: [$F_{1,5}$=39.954, P=0.001]; 500 μM DOSE: [$F_{1,5}$=26.980, P=0.003]) and those seen following the lowest (100 μM) dose (250 μM DOSE: [$F_{1,5}$=19.137, P=0.007]; 500 μM DOSE: [$F_{1,5}$=9.447, P=0.028]). The lowest (100 μM) dose did not significantly increase ACh over vehicle (all Ps>0.05). ACh efflux returned to basal levels 30 min following the removal of the drug [all Ps>0.05].

Perfusion of carbachol into PFC also dose-dependently increased ACh efflux locally within the PFC (DOSE [$F_{3,15}$=8.747, P=0.004]; TIME [$F_{6,30}$=11.812, P=0.008]; DOSE×TIME [$F_{18,90}$=6.816, P=0.001]), with the maximum effect after 105 min of drug administration (1849%±515; Fig. 5, top panel). PFC ACh efflux returned to basal levels 30 min following the removal of the drug (all Ps>0.05).

Effects of intra-PFC nicotine on ACh efflux in PPC

Basal ACh efflux. Basal efflux of ACh in PPC (n=5) did not significantly differ across doses or sessions (all Ps>0.05). Thus, subsequent analyses were conducted on data expressed as percent change from mean baseline as shown in Fig. 4 (bottom panel). Basal release of ACh (fmol/15 μl sample) in the PPC for each condition was vehicle: 17.3±6.6; 1 mM nicotine: 23.9±8.6; 5 mM nicotine: 8.5±2.8; 10 mM nicotine: 7.6±2.4.

Nicotine-stimulated ACh efflux. The effects of nicotine perfused into the PFC on ACh efflux in PPC are shown in Fig. 4 (bottom panel). Nicotine did not affect ACh efflux at any dose tested (all Ps>0.05). Thus, in contrast to carbachol, administration of nicotine into the PFC produced no significant variation in ACh efflux distally in the PPC.

However, nicotine dose-dependently increased local prefrontal ACh efflux (DOSE [$F_{3,12}$=10.974, P=0.017]; TIME [$F_{6,24}$=24.178, P=0.000]; DOSE×TIME [$F_{18,72}$=4.721, P=0.000]), reaching the maximum effect after 90 min of drug perfusion (1646%±315; Fig. 5, bottom panel). ACh efflux did not differ from baseline across doses 30 min following drug removal (DOSE: [$F_{3,12}$=2.656, P=0.096]; DOSE×TIME: [$F_{6,24}$=2.332, P=0.100]). These results indicate a dose-dependent increase in cortical ACh efflux in the PFC following local administration of nicotine in the PFC that is similar in magnitude to that of the local effects of carbachol outlined above, despite a lack of effect of intra-PFC nicotine administration on distal PPC ACh efflux.

Effects of intra-PFC carbachol/antagonist co-administration on ACh efflux in PPC

Basal ACh efflux. Basal ACh efflux (n=7) in PPC did not vary across drug condition or by dialysis session (all Ps>0.05). The means for basal ACh efflux (fmol/15 μl sample) in each condition were 500 μM+vehicle: 12.3±2.0; 500 μM carbachol+100 μM atropine: 8.0±3.7; 500 μM carbachol+100 μM mecamylamine: 12.4±2.9; 500 μM carbachol+100 μM DNQX: 10.6±2.4.

ACh efflux following carbachol/antagonist co-administration. The effects of 500 μM carbachol alone or carbachol co-perfused with an antagonist into the PFC on ACh efflux in the PPC are shown in Fig. 6. Administration of the antagonists alone following the baseline period, and prior to the addition of carbachol, did not significantly affect ACh efflux compared with basal levels (all Ps>0.05). The overall analysis of the drug co-administration period indicated that one or more antagonists significantly attenuated the effects of carbachol perfusions into PFC (DRUG [$F_{3,18}$=3.926, P=0.062]; TIME [$F_{5,30}$=8.303, P=0.000]; DRUG×TIME [$F_{15,90}$=2.027, P=0.037]). The administration of atropine in conjunction with carbachol significantly attenuated the increase in PPC ACh efflux produced by carbachol alone (DRUG [$F_{1,6}$=5.972, P=0.050]). DNQX co-administration with carbachol also attenuated carbachol-induced ACh efflux over time (TIME: [$F_{5,30}$=10.473, P=0.000]; DRUG×TIME: [$F_{5,30}$=2.624, P=0.044]. Mecamylamine co-administration, however, did not significantly attenuate the effect of carbachol alone (P>0.05). ACh efflux following drug removal was not different from baseline across antagonist conditions (DOSE: [$F_{3,18}$=0.594, P=0.626]; DOSE×TIME: [$F_{6,36}$=0.124, P=0.993]).

Effects of drug administration into the PPC on ACh efflux in PFC

Basal ACh efflux in PFC (n=7) did not differ across drug treatment conditions or dialysis sessions (all Ps>0.05). The means for the basal release of ACh (fmol/15 μl sample) in the PFC for each condition were vehicle: 7.1±1.8; 50 μM AMPA: 7.2±1.6; 10 mM nicotine: 3.9±1.2; 500 μM carbachol: 10.0±3.8.

Effects of drug administration in PPC on ACh efflux in PFC

The effects of intra-PPC perfusion of the highest doses of carbachol, nicotine, and AMPA (from previous experiments) on PFC ACh efflux are shown in Fig. 7 (top panel). None of the drug perfusions resulted in significant changes in PFC ACh efflux in PFC (all Ps>0.05).

It is important to note that administration of nicotine and carbachol into the PPC significantly increased local ACh efflux (DRUG [$F_{3,18}$=6.128, P=0.047]; TIME [$F_{6,36}$=

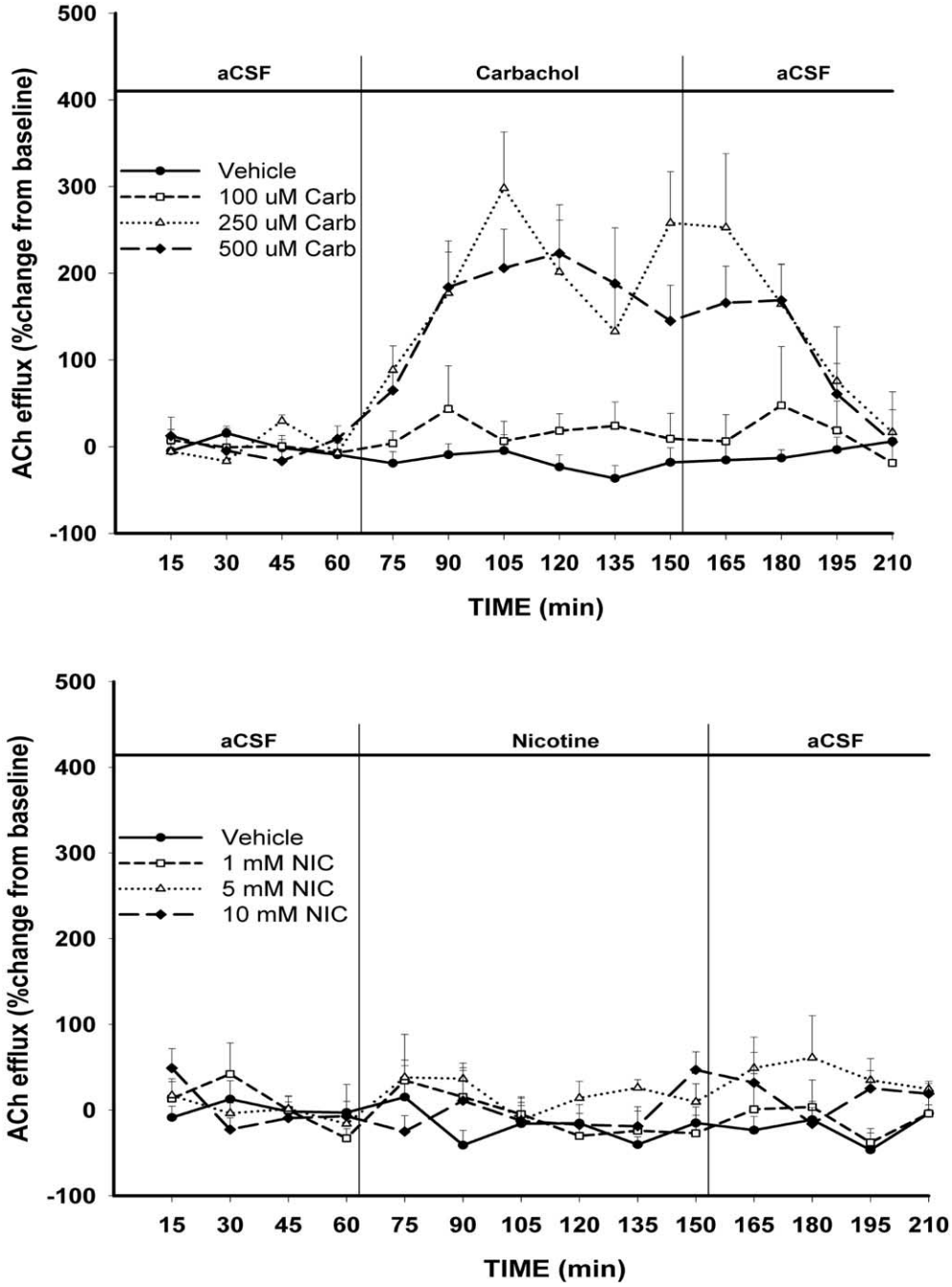

Fig. 4. Mean (±S.E.M.) ACh efflux (% change from mean baseline) in the PPC of animals receiving carbachol (n=6, top panel) or nicotine (n=5, bottom panel) into the PFC. For each experiment, all animals received all treatments in counterbalanced order. Following baseline collections (0–60 min), carbachol or nicotine was administered in the PFC via reverse dialysis, and 90 min of drug perfusion collections were taken. Drug was then removed from the PFC, and 60 min of post-drug collections were taken. The two highest doses of carbachol tested (250 μM [triangles] and 500 μM [diamonds]) resulted in significant increases in ACh efflux in the PPC. No dose of nicotine tested resulted in any significant increase in PPC ACh efflux.

3.714, P=0.048]; DRUG×TIME [$F_{18,108}$=2.782, P=0.088]; Fig. 7, bottom panel). The local effects of both carbachol (954%±325) and nicotine (5897%±3047, large variation reflected an unusually elevated response from one animal) reached a maximum after 75 min of drug administration. ACh efflux did not differ from baseline 30 min following drug removal (all Ps>0.05). By contrast, PPC administration of AMPA (50 μM) did not significantly increase local PPC ACh efflux.

Collectively, these results indicate that the cholinergic agonists produced significant local increases in ACh efflux when perfused into the PFC or the PPC, and these effects were similar in magnitude, despite the fact that these drugs were ineffective at producing distal effects in PFC.

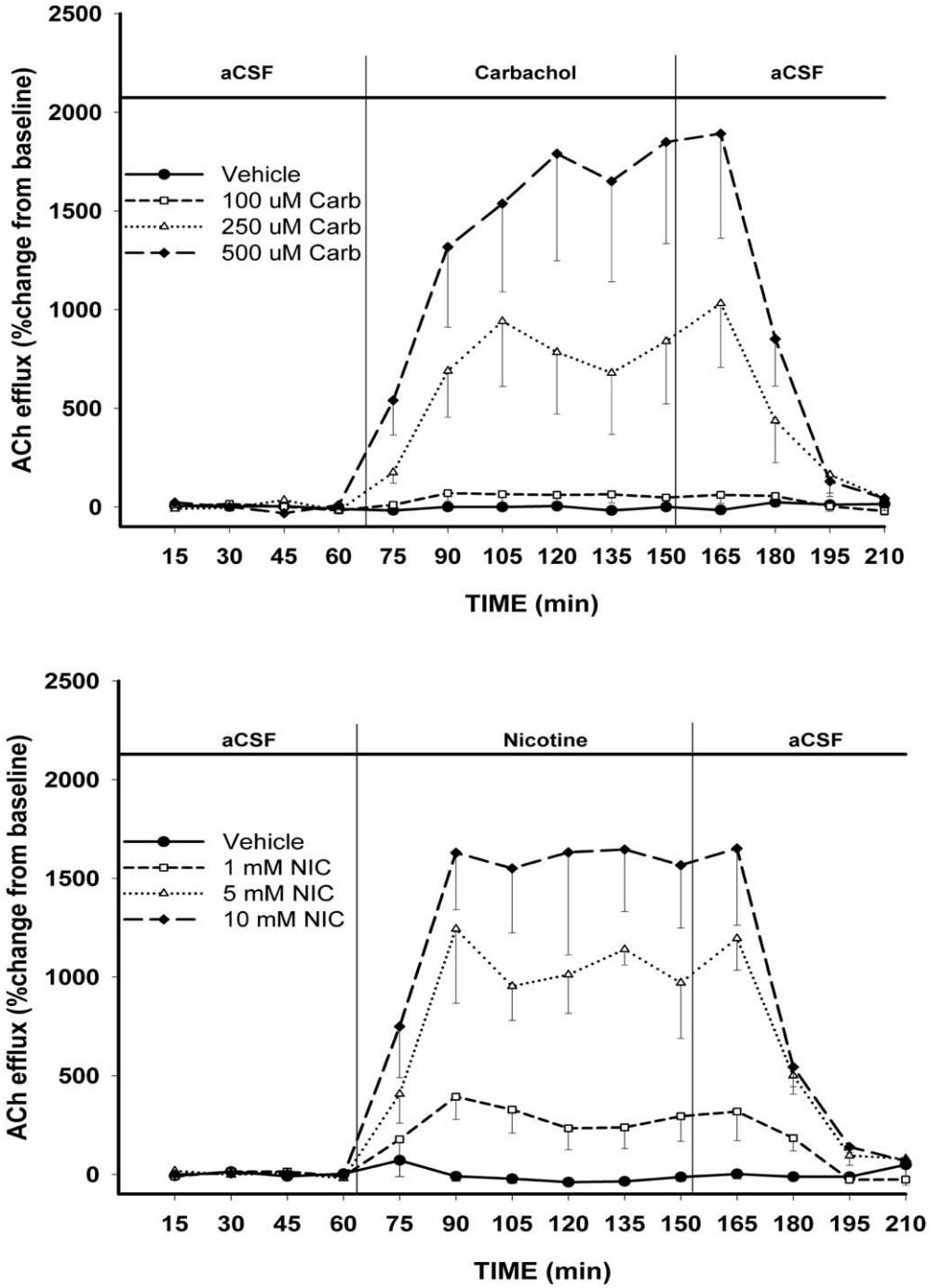

Fig. 5. Mean (±S.E.M.) ACh efflux (% change from mean baseline) in the PFC of animals (n=6) receiving carbachol (top panel) or nicotine (n=5, bottom panel) into the PFC. For each separate experiment, all animals received all treatments in counterbalanced order. Following baseline collections (0–60 min), drug was administered in the PFC via reverse dialysis, and 90 min of drug perfusion collections were taken. Drug was then removed, and 60 min of post-drug collections were taken. As shown in the top panel, the two highest doses of carbachol tested (250 μM [triangles] and 500 μM [diamonds]) resulted in robust increases in ACh efflux in the PFC. As shown in the bottom panel, the two highest doses of nicotine tested (5 mM [triangles] and 10 mM [diamonds]) produced robust increases in local PFC ACh efflux similar in magnitude to those of carbachol.

DISCUSSION

The present experiments were designed to determine if glutamatergic and cholinergic mechanisms within the PFC contribute to the regulation of posterior parietal cholinergic transmission. A role for glutamatergic regulation was supported by the observation that administration of AMPA, but not NMDA, into the PFC increased ACh efflux in the PPC. Administration of DNQX in conjunction with AMPA blocked the effects of AMPA on ACh efflux in the PPC. Cholinergic antagonists (muscarinic or nicotinic) did not significantly

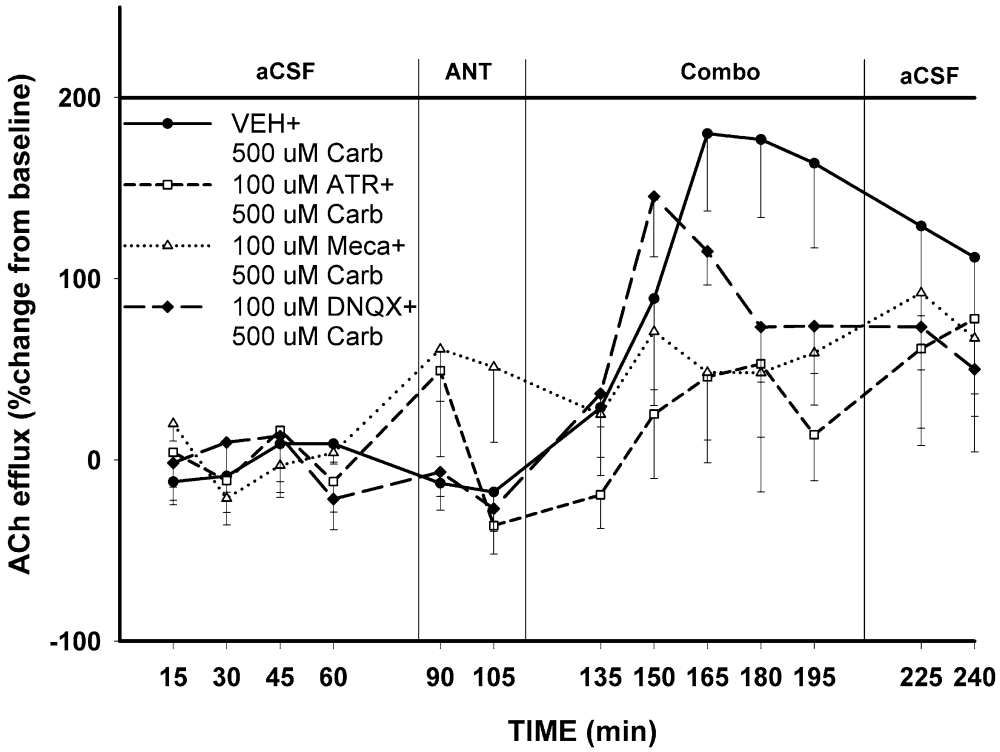

Fig. 6. Mean (±S.E.M.) ACh efflux in the PPC of animals (n=7) receiving co-administration of an antagonist (VEH, atropine, mecamylamine, DNQX) and 500 μM carbachol in the PFC. All animals received all treatments in counterbalanced order. Following baseline collections (0–60 min), animals received antagonist or vehicle into the PFC for 30 min. This was followed by antagonist+carbachol co-administration for 75 min, and the removal of drug for 45 min of collections at the conclusion of the testing period. Co-administration of atropine (squares) significantly attenuated the carbachol-induced ACh increase in the PPC. Mecamylamine (triangles) and DNQX (diamonds) co-administration produced moderate attenuation of the carbachol-induced ACh increase, but these changes were not statistically significant.

attenuate the effects of AMPA. A role for cholinergic regulation was supported by the observation that perfusions of carbachol, but not nicotine, increased ACh efflux in PPC. This carbachol effect was attenuated by co-administration of the muscarinic receptor antagonist atropine and partially by the nicotinic receptor antagonist mecamylamine or the AMPA receptor antagonist DNQX. Finally, while both carbachol and nicotine perfusions into PPC resulted in significant increases in ACh efflux locally, neither PPC drug perfusions produced any alteration in PFC ACh efflux. The discussion that follows will focus on putative mechanisms underlying these regulations, methodological issues surrounding the interpretation of these results, and the functional implications of prefrontal modulation of posterior parietal transmission.

Glutamatergic regulation of cortical ACh release

The observation that intra-PFC perfusions of AMPA result in a stimulation of ACh release distally within the PPC is a novel observation and illustrates the capacity of prefrontal regions to regulate more broadly the activity of the cholinergic input system elsewhere in the cortex. In fact, the magnitude of increase in ACh efflux was larger in the distal PPC site than locally in the PFC. This differential increases may reflect the possibility that the distal increases in ACh efflux are a combined result of activation of corticofugal projections to the basal forebrain (Zaborszky et al., 1997) that may yield increases in ACh release throughout cortex, including PPC, and of direct cortico-cortical projections that may stimulate ACh efflux in the PPC via synaptic mechanisms. The present approach did not permit the determination of the relative contributions of these two circuits to increases in PPC ACh release (see below for additional discussion).

In contrast to the fast excitatory transmission mediated by AMPA receptors, activation of the voltage-dependent NMDA receptor did not result in increased ACh release either locally in PFC or distally in PPC. The lack of effect following NMDA was not unexpected as the present experiments assessed drug effects on basal ACh efflux and did not incorporate activating manipulations that would sufficiently depolarize NMDA receptors and thus allow the demonstration of effects of NMDA perfusions. NMDA receptors are located mainly on cortico-cortical projections in layers II and III (Miller, 1996; Monaghan and Cotman, 1985) and exhibit relatively low levels of basal activity (Miller, 1996). Our research on the ability of NMDA receptors to locally regulate basal forebrain excitability is consistent with the negative results reported here. Intra-basalis infusions of NMDA were ineffective in stimulating cortical ACh release in rats under basal conditions. However, following activation of the animal with an environmental stimulus (turning lights off), previously ineffective doses of NMDA then stimulated the BFCS (Fadel et al., 2001). It remains to be seen whether

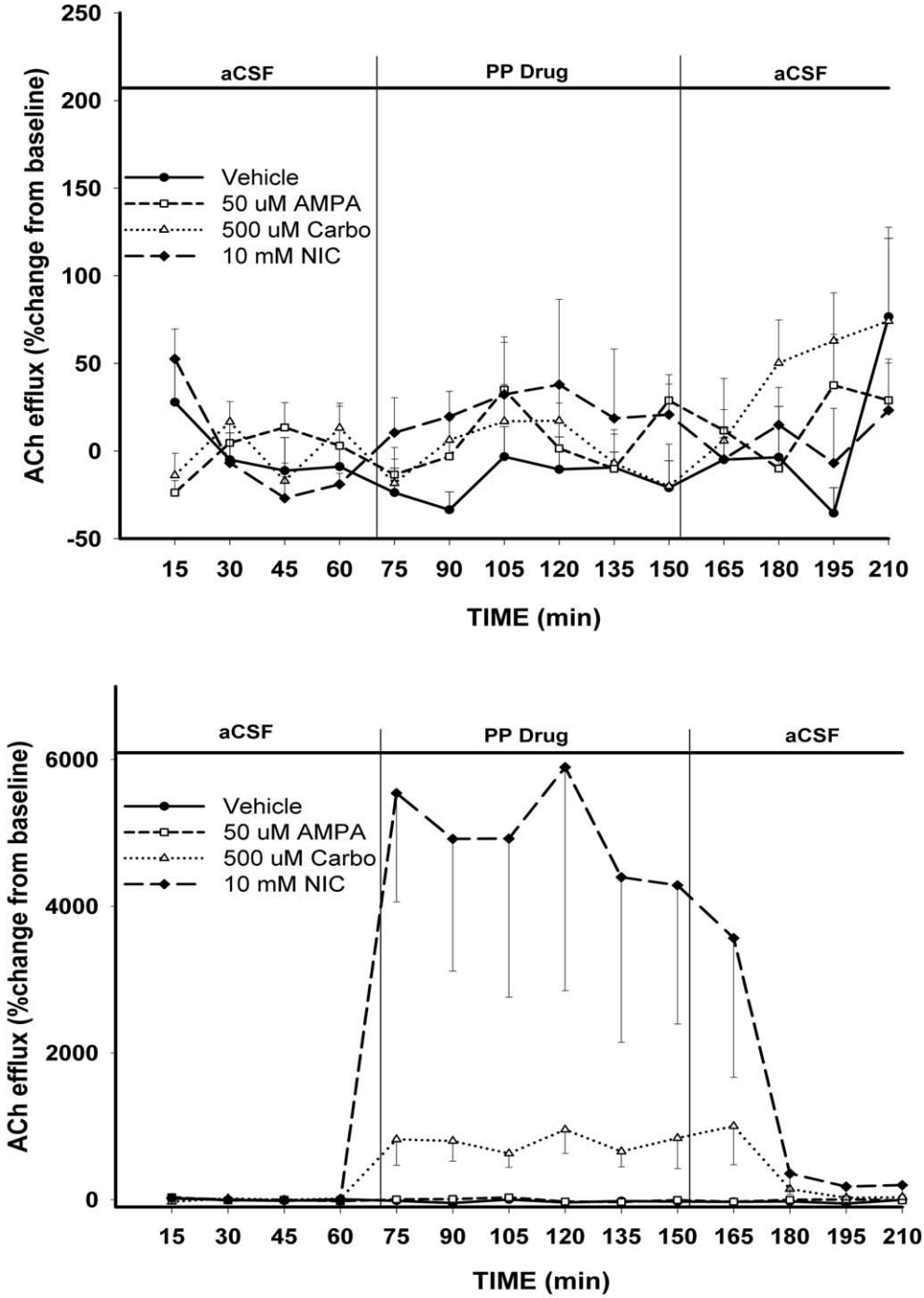

Fig. 7. Mean (±S.E.M.) ACh efflux (% change from mean baseline) in the PFC (top panel) or PPC (bottom panel) of animals ($n=7$) receiving AMPA (squares), carbachol (triangles), or nicotine (diamonds) into the PPC. All animals received all treatments in counterbalanced order. No drug tested significantly affected ACh efflux in the PFC (top panel). In contrast, nicotine or carbachol ($n=7$), but not AMPA, perfusions into the PPC (bottom panel) resulted in large increases in local ACh efflux, comparable to those seen following local perfusions into the PFC (see Fig. 5).

NMDA into the PFC in animals activated in some fashion would then result in increased ACh release in local and distal cortical sites.

The potent attenuation of AMPA-induced cortical ACh release in PPC following PFC perfusion of DNQX supports the interpretation that, in awake but passive animals, this effect is driven by stimulation of non-NMDA glutamate receptors. In contrast, co-administration of a muscarinic or nicotinic antagonist was without effect, suggesting that an increase in local cholinergic receptor activity is not necessary for AMPA-induced increases in ACh release in PPC. It remains possible that higher concentrations of atropine or mecamylamine would suppress the AMPA effect. However, the concentrations of these antagonists utilized in

this experiment were effective in attenuating the stimulating effects of the mixed cholinergic agonist carbachol.

Cholinergic regulation of cortical ACh release

The administration of carbachol or nicotine into the PFC resulted in comparable and potent increases in local cortical ACh efflux. The local stimulation following these agonists was not unexpected given previous demonstrations that intra-cortical administration of nicotine stimulates ACh efflux *in vivo* (Summers and Giacobini, 1995) and in cortical slices (Marchi and Raiteri, 1996). Because carbachol is a mixed muscarinic and nicotinic agonist the sufficiency of muscarinic receptor activation for this effect cannot be determined. Moreover, the present study cannot differentiate the relative contributions of nicotinic receptor subtypes in cortex ($\alpha_4\beta_2$ and α_7) to the nicotine effect. The answers to these important questions must await the use of a more selective muscarinic agonist with solubility more suitable for microdialysis studies than those currently available. In contrast to their effects on local ACh release, the effects of carbachol and nicotine were readily dissociated with respect to their effects distally in PPC. The perfusion of carbachol into PFC resulted in a significant increase in ACh efflux in PPC whereas perfusion of nicotine was without effect. This dissociation suggests that muscarinic receptor stimulation or the simultaneous activation of muscarinic and nicotinic receptors is necessary for the prefrontal cholinergic regulation of ACh release in PPC.

As is the case with the effects of glutamate ligands, the roles of muscarinic and nicotinic receptors in regulating cortical ACh release remain poorly understood. Stimulation of M_1 receptors in PFC has been shown to increase both glutamate and GABA release (Sanz et al., 1997). Thus, carbachol-mediated increases in glutamate transmission might be expected to stimulate PFC AMPA receptors and eventually lead to ACh release in PPC (as described above). This scenario is also consistent with the observation that DNQX was partially effective in attenuating the carbachol effect on ACh release. Carbachol-mediated stimulation of GABA receptors might also contribute to the stimulation of cortical ACh release via multi-synaptic effects on inhibitory interneurons. We are currently conducting studies examining the effects of intra-PFC perfusion of the GABA antagonist bicuculline on carbachol-mediated ACh efflux in both PFC and in PPC.

The co-administration of carbachol and various receptor antagonists suggests a cascade of events responsible for its distal effects in PPC. The ability of atropine to attenuate markedly the stimulated release of ACh highlights the prominent role of muscarinic receptors in initiating this sequence. M_1 receptors are believed to be the major class of post-synaptic receptors in cortex and future studies will aim to utilize selective M_1 ligands to study these mechanisms.

Co-administration of mecamylamine appeared to attenuate the ability of carbachol to stimulate ACh efflux in PPC (Fig. 6), although this effect, which was not significant (due to large variability), was not as great as that seen following co-administration of atropine. However, even a partial attenuation following mecamylamine is surprising given the complete inability of local perfusion of nicotine to affect cholinergic transmission in PPC. These findings suggest that activation of both muscarinic and nicotinic receptors in PFC contributes to the ability of carbachol to stimulate ACh release in PPC, but, that the muscarinic component is the predominant of the two receptor subtypes. Thus, stimulation of nicotine receptors in PFC is not sufficient to stimulate ACh release in PPC in the absence of simultaneous stimulation of muscarinic receptors. While plausible, this hypothesis does not resolve the paradox that nicotine, in stimulating *local* ACh release in PFC would, presumably, also indirectly result in an activation of muscarinic receptors, yet there is no change in ACh release in PPC. Clearly, additional studies with more selective agonists and antagonists will be required in order to identify the relative contributions of muscarinic and nicotinic receptors, and their multiple subtypes, to the carbachol and nicotine effects.

The ability of the non-NMDA antagonist DNQX to partially attenuate the ability of carbachol to stimulate ACh release in PPC is intriguing and suggests the possibility that the actions of carbachol might ultimately involve an activation of non-NMDA receptors. This would be consistent with the previously discussed ability of AMPA to stimulate ACh release in PPC. It would also be consistent with observations that local administration of muscarinic (Sanz et al., 1997) and nicotinic (Gioanni et al., 1999) agonists can increase glutamate release in cortex.

Functional implications

The PFC and PPC, and the cholinergic projections to these cortical regions, are integral parts of a larger distributed neuronal network mediating attentional functions. In addition to PFC inputs (Zaborszky et al., 1997), afferent input to the basal forebrain arises from the nucleus accumbens (Zaborszky and Cullinan, 1992), locus coeruleus (Jones and Cuello, 1989), and amygdala (Jolkkonen et al., 2002), indicating a diverse regulation of basal forebrain excitability. While the present results might highlight the ability of glutamatergic and cholinergic mechanisms within PFC to regulate ACh release in another cortical area, the current experiments were not designed to isolate which inputs to the basal forebrain or PPC were involved in producing the changes in PPC ACh efflux following PFC drug perfusions. Future research will be directed toward dissociating the contributions of PFC-cortical versus PFC-BFCS projections to increases in PPC ACh efflux.

The demonstrated ability of the PFC to regulate transmission in more posterior cortical regions such as PPC may represent a mechanism that contributes to the “top-down” control of attention (Sarter et al., 2001, 2005). For example, prefrontal cholinergic inputs mediate the effects of a distractor in animals performing a sustained attention task (Gill et al., 2000). In order to limit the detrimental performance effects of a continuing distractor, and to regain stable performance, the processes that mediate the detection and discrimination of signals require optimization, most likely by enhancing the cholinergic processing of sensory inputs in cortical sensory and sensory-associational regions (Sarter et al., 2005). The

present data suggest that prefrontal regions are capable of influencing posterior cortical regulation of ACh release. This mechanism may be employed to counteract, for example, the consequences of a distractor. Recent data further suggest that prefrontal ACh efflux and choline transporter capacity are enhanced by increased demands on attentional performance (Kozak et al., 2004; Apparsundaram et al., 2004). Again, these prefrontal increases in ACh efflux are likely to influence the activity of cholinergic inputs elsewhere in the cortex, thereby mediating the changes in input processing functions that allow the animals to cope with increased demands on attentional performance (Sarter et al., 2001, 2005). We are currently exploring these hypotheses in complex experiments in which animals, performing in attentional tasks, are being dialyzed with probe placements in various cortical regions.

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