Iranian Journal of Basic Medical Sciences
Vol. 11, No. 4, Winter 2009, 221-228
Received: Sep 16, 2008; Accepted: Dec 27, 2008

IJBMS

Original article

Modulation of Basal Glutamatergic Transmission by Nicotinic Acetylcholine Receptors in Rat Hippocampal Slices

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Abstract

Objective(s)
Nicotinic acetylcholine receptors (nAChRs) regulate epileptiform activity and produce a sustained pro-epileptogenic action within the hippocampal slices. In the present study, we investigated the effect of nAChRs on evoked glutamatergic synaptic transmission in area CA3 and CA1 of rat hippocampal slices to identify possible excitatory circuits through which activation of nAChRs produce their pro-epileptogenic effects.
Materials and Methods
Hippocampal slices (400 µm thick) prepared *in vitro* from male Wistar rats (3-5 weeks), using standard procedures. Following 1 hr equilibration in artificial cerebrospinal fluid (ACSF), slices transferred to an interface recording chamber. Stimulatory electrodes placed within the hilus or Schaffer-collateral pathways and extracellular field recordings made in the *stratum radiatum* of the CA1 and CA3 regions to investigate evoked synaptic responses.
Results
Bath application of the selective nAChR agonist dimethylphenyl-piperanzinium (DMPP, 30 µM) resulted in a sustained and reversible enhancement of glutamate afferent evoked fEPSP amplitude by 15.7±5.1% (mean±SEM; n=8 of 12) in the CA3 region of the hippocampus but not in the CA1 (-5.25±8.3%, mean±SEM; n=5).
Conclusion
Activation of nAChRs may produce pro-epileptogenic actions in part through regulating glutamatergic circuits. Difference in nAChR regulation is also evident between different regions of hippocampus.

Keywords: Acetylcholine, Epilepsy, Glutamate, Hippocampus, Nicotinic receptor

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Introduction

Nicotinic acetylcholine receptors (nAChRs) are ligand–gated ion channels that have been implicated in a variety of brain functions, depending on nAChR subtype and their location, as well as pathological states (1). Located at both pre, post and extra-synaptic sites, nAChRs are ideally placed to regulate neuronal excitability in the CNS. In the hippocampus, nAChRs are present on surface of both GABAergic inhibitory interneurons (2-7) and the excitatory glutamatergic pyramidal cells (4, 8, 9), modulating both inhibitory and excitatory circuits. Although pyramidal cells do express nicotinic receptors their role is thought to be presynaptic, important in the modulation of neurotransmitter release (4, 10, 11) which is believed to be mediated via an increase in presynaptic Ca^{2+} influx (10, 12-14). A postsynaptic nicotinic response from pyramidal cells has been the subject of an ongoing dispute with most previous studies reporting that pharmacological activation of nAChRs do not produce any form of membrane potential response in these cells (6, 15).

Cortical areas are a common site for genesis of seizure activity and many studies suggest that nAChRs are implicated in seizure generation (16, 17) and may be important in certain forms of epilepsy (18-21). We have recently shown pharmacological activation of nAChRs to produce a sustained pro-epileptogenic action within the hippocampal slice (22). However, the mechanism underling the role of nAChRs in patterning epileptiform activity is poorly understood. Since nAChRs produce a similar phenotype of modulation in different pharmacological epileptiform models, it is possible that nAChRs target a common cellular mechanism that is prevalent in each model. In this respect, a potentially important locus of action is likely to be the recurrent glutamatergic synapses in area CA3, since these recurrent connections are believed to be critical in the generation and regulation of bursting activity within the CA3 network (23-25). All these taken together prompted us to investigate the role of nAChRs in the modulation of synchronous excitatory potentials in rat hippocampal slices. We therefore, assessed the effects of nAChR activation on evoked glutamatergic synaptic transmission on hippocampal CA3 and CA1 areas, to investigate possible glutamate circuits involved in nAChRs-induced pro-epileptogenic effects.

Materials and Methods

Drugs

1, 1-dimethyl-4-phenyl-piperazium iodine (DMPP) was purchased from Sigma (Poole, UK). 6-nitro-7-sulphamoylbenzo[*f*]quinoxaline-2,3-dione (NBQX) purchased from Research Biochemicals International (Natick, MA, USA.); and D-(*E*)-2-Amino-4-methyl-5-phosphono-3-pentanoic acid (CGP 40116), was gift from Dr Kumlesh Dev, Novartis Pharmaceuticals, Basel, Switzerland.

Slice preparation

Experiments performed on transverse hippocampal slices obtained from male Wistar rats (3-5 weeks old). Following cervical dislocation, animals decapitated in accordance with UK Home Office Guidelines. The brain removed rapidly and immersed in a beaker containing chilled artificial cerebrospinal fluid (ACSF). Transverse horizontal slices prepared as described previously (26) by hemisecting whole brain minus the cerebellum and cutting 400 μm thick transverse slices, using a vibrating microtome (Leica VT1000, Milton Keynes, UK). The hippocampal formation cut free from the surrounding brain areas, using a scalpel blade and the resultant slices placed on a lens tissue at the interface of a warmed (32-34 °C) artificial cerebrospinal fluid (ACSF, perfusion rate 1-2 ml/min) and an oxygen-enriched (95% O_2, 5% CO_2), humidified atmosphere. The standard perfusion medium (ACSF) comprised (mM): NaCl, 124; KCl, 3; $NaHCO_3$, 26; NaH_2PO_4, 1.25; $CaCl_2$, 2; $MgSO_4$, 1; D-glucose, 10; and bubbled with 95% O_2, 5% CO_2. Spare slices stored submerged in carboxygenated standard ACSF at room temperature.

Electrophysiology

Recording electrodes pulled from the standard wall borosilicate tubing, using a Brown and Flaming type horizontal electrode puller (Sutter Inst, USA). Extracellular recording electrodes filled with ACSF and exhibited a dc resistance of 1-5 MΩ. Slices allowed equilibrating in the recording chamber for at least one hr before recording commenced. The recording electrodes placed on the surface of the slice in the *stratum radiatum* of the CA3 and CA1 regions. Stimuli delivered of 20 sec intervals via the bipolar stimulation electrode positioned within the hilus or Schaffer collaterals pathways and the resulting field excitatory post synaptic potentials (fEPSPs) recorded. The stimulus comprised of a square wave pulses of 20 µsec duration and 0-30 mA constant current amplitude. The stimulus intensity adjusted to evoke a response of half of the maximum response value for each experiment (range 1.2-2.5 mA).

All recordings performed under current clamp conditions and signals amplified using an Axoclamp 2B amplifier (Axon Instruments, USA) operated in bridge mode. Signals further amplified and conditioned, using a Brownlee Model 440 signal processor (Brownlee Inst, San Jose, CA, USA) and data captured directly onto a PC hard disk, using pClamp 8.0 software (Axon Instruments, CA, USA). Analysis carried out off-line using pClamp8, Graph Pad Prism and InStat version 3.05 (GraphPad Software, San Diego, CA, USA), software packages.

Data are presented as means±standard error of the means (SEM) and statistical significance determined, using Paired t-tests and ANOVA performed on raw data with $P<0.05$ being taken as indicating statistical significance. The number of times a particular experiment was repeated shown as n values.

Results

Effect of nAChR activation on evoked glutamatergic synaptic transmission on area CA3

To investigate the action of nAChRs on basal glutamatergic transmission, field EPSPs (fEPSPs) recorded in the CA3 region of the hippocampal slices, placing recording electrode in the stratum radiatum of the CA3 region and stimulatory electrode within the hilus. Typically, fEPSPs evoked by local electrical stimulation consisted of a compound glutamatergic EPSP, mediating by the activation of AMPA/Kainate and NMDA receptors. Figure 1A shows a representative example of a fEPSP recorded from the CA3 region on which specific glutamatergic antagonists tested. Bath application of the AMPA/Kainate receptor antagonist, NBQX (2 µM) decreased the amplitude of the EPSP (Figure 1A2) and the further addition of the NMDA receptor antagonist CGP40116 (50 µM) completely abolished the EPSP (Figure 1A3), demonstrating the mixed NMDA and AMPA/Kainate-mediated nature of the evoked synaptic response.

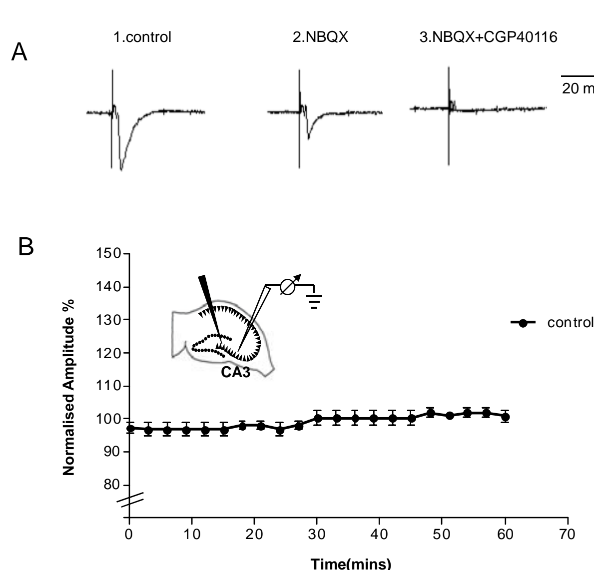

Figure 1. Glutamategic nature of the evoked synaptic response.
A. Example traces of the response evoked by electrical stimulation in the hilus region (1) before and (2) during superfusion with NBQX (2iM) alone and (3) combined application of NBQX and CGP40116 (50 iM). Note complete abolishment of EPSP following combined application of glutamatergic antagonists. B. Timeplot showing mean evoked EPSP amplitude in areas CA3 under control condition (drug free condition, n=5), at an intensity producing half of the maximum response. Note the stability of evoked EPSPs amplitude that persisted for long periods.

Initial experiments were to investigate the stability of evoked fEPSPs in area CA3. In order to ensure that the amplitude of the

evoked EPSPs on area CA3 remains stable over the period of experiments, control fEPSPs recorded in the absence of any drug. As illustrated in Figure 1B, electrical stimulation of afferent fibers within the hilar region resulted in the occurrence of a stable EPSP in area CA3, which was sustained and stable for the extended duration of the experiments (up to 60 min, n=5, Figure 1B).

In the next set of experiments, a selective nAChR agonist 1, 1-dimethyl-4-phenyl-piperazium iodine (DMPP, 30 μM) applied following a stable EPSP baseline, to investigate the effect of nAChRs on evoked glutamatergic synaptic transmission in area CA3. The slices stimulated once every 20 sec for a period of 20-30 min before, during and after superfusion with DMPP. Bath application of 30 μM DMPP resulted in a sustained and reversible enhancement of glutamate afferent evoked fEPSP amplitude by 15.7±5.1% (mean±SEM; *P*=0.007, One-way ANOVA) in the CA3 region of the hippocampus (Figure 2 A-B, n=8 of 12). These data suggest that glutamatergic transmission is enhanced by nAChR activation in the CA3 region of the hippocampus.

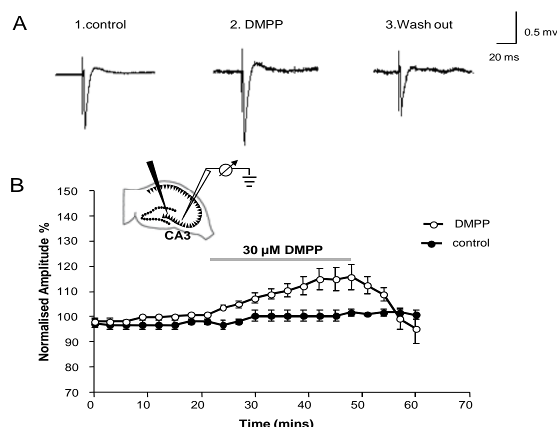

Figure 2. Effect of DMPP on field EPSPs (fEPSPs) recorded in the CA3 stratum radiatum of rat hippocampal slice preparation.
A. Example traces of the evoked fEPSPs in area CA3 before (1), during (2), and after (3) superfusion with DMPP (30 μM). Note the reversible increase in the amplitude of EPSP in the presence of DMPP. B. Timeplot showing mean evoked EPSP amplitude in areas CA3 upon application of DMPP (30 μM, horizontal bar, n=12) and in area CA3 under control condition (n=5), all at an intensity producing half of the maximum response. Note the reversible increase in the evoked EPSP amplitude in area CA3 (n=8 of 12) following DMPP application.

The Effect of nAChR activation on the amplitude of fEPSPs recorded in area CA3 assessed at varying stimulus intensities. The result of DMPP action on such stimulus-responses is given in Figure 3. Paired t-tests performed on raw data at each point, revealing that fEPSP amplitudes significantly increased from baseline following DMPP application only at lower (1 and 2 mA) stimulus intensities (*P*<0.05). There were no significant changes in other intensities.

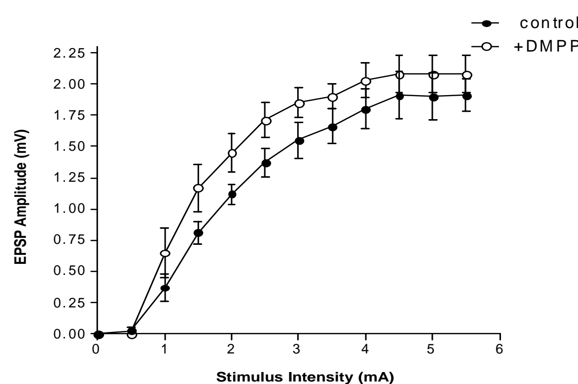

Figure 3. Effect of DMPP on the amplitude of fEPSPs recorded in area CA3 using different intensities.
Data are plotted as mean across all intensities±SEM. Each point represents the average for 4 experiments. Note the clear upward shift in the curve upon DMPP application.

Effect of nAChR activation on evoked glutamatergic synaptic transmission on area CA1

Addition experiments carried out in area CA1. Field EPSPs recorded in the CA1 region of the hippocampus by placing recording electrodes within the *stratum radiatum* towards the middle of the CA1 region and subsequently stimulating the Schaffer collaterals with stimulation electrode placed within the *stratum radiatum* close to the CA3/CA1 border. DMPP (30 μM) applied to the bath once stable EPSP baseline amplitude achieved. In contrast to findings in area CA3, no significant change (-5.25±8.3%, mean±SEM; *P*=0.4, One-way ANOVA) observed on fEPSPs recorded in the CA1 region (Figure 4 A-B, n=5) upon application of DMPP, suggesting that application of the nicotinic agonist does not alter glutamate transmission at this synaptic connection.

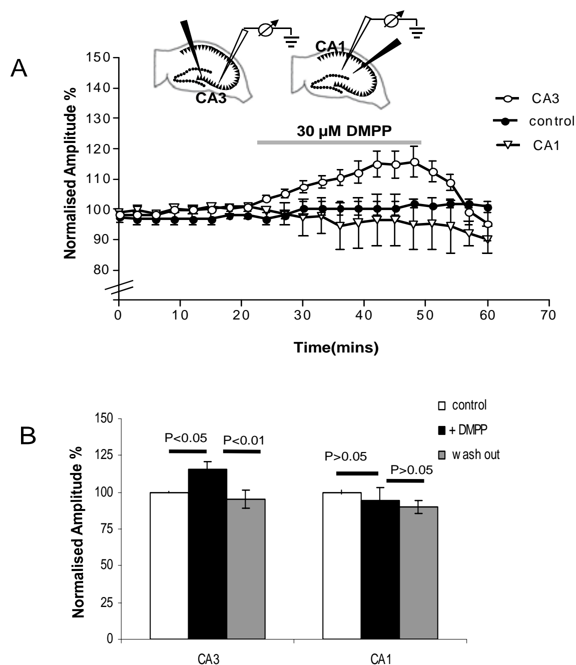

Figure 4. Comparison of Effect of DMPP on field EPSPs (fEPSPs) recorded in the CA3 and CA1 stratum radiatum of rat hippocampal slice preparation.
A. Timeplot comprising mean evoked EPSP amplitude in areas CA3 and CA1 upon application of DMPP (30 μM, horizontal bar, n=12 for CA3, n=5 for CA1) and in area CA3 under control condition (no DMPP added, n=5), all at an intensity producing half of the maximum response. Note the reversible increase in the evoked EPSP amplitude in area CA3 (n=8 of 12) following DMPP application but no consistent change in area CA1 (n=5) following DMPP application. B. Histogram summarising DMPP-induced change in fEPSP amplitude. One-way ANOVA indicated a significant increase in the CA3 region (P=0.007) but not in area CA1 (P=0.4).

Discussion

The main finding of this study is that application of selective nAChRs agonist DMPP results in a sustained and reversible enhancement of glutamate afferent evoked fEPSP amplitude in the CA3 region of the hippocampus. These data suggest that glutamatergic transmission is enhanced by nAChR activation in the CA3 region of the hippocampus. In 1995, McGehee *et al* showed that nicotine enhanced glutamate transmission in the habenula nucleus of chick (27). This finding is further supported by the observation reported that nicotine increased the frequency of mini EPSPs in the CA3 region of the hippocampus and hippocampal cell cultures (10, 28). These published results and aspects of the present data indicate that nAChRs may enhance glutamate release from presynaptic terminals.

In our experiments, increasing the stimulus intensity also increased the amplitude of the evoked EPSP. This presumably reflects the fact that an increase in stimulation intensity would ultimately recruit more fibres and subsequently increase the amount of synaptically released glutamate. Nevertheless, in our experiments, it was not possible to indicate precisely pre- or post-synaptic origin of nicotinic effect. Field EPSP amplitude represent the magnitude of synaptic activation (29) and as this variable was enhanced by DMPP, a general enhancement of glutamate release is suggested.

Data showing modest but significant increase in the amplitude of evoked EPSPs in the presence of DMPP compared with the control is consistent with a general enhancement of glutamate release across a population of glutamatergic terminals although it is not possible to exclude the possibility of other less direct effect through other systems and transmitters, notably GABA (14, 30). Such a finding has been described by Mann and Greenfield (2003) who showed that the inhibition of NMDA receptors revealed a long-lasting excitatory effect of nicotine on hippocampal activity which appeared to be mediated via GABAergic interneurons (30). As our evoked EPSP experiments were not carried out in the presence of GABA receptor antagonists, it is not possible to conclude whether nAChRs modulation is via a direct action on glutamatergic transmission or via a more indirect mechanism, possibly through regulation of GABAergic circuits. However, such an action of nAChRs appears to be independent of fast GABAergic transmission, as detailed previously (22), at least with respect to the pro-epileptogenic action. An important finding in this respect was that nAChR activation also resulted in a facilitation of epileptiform burst discharge in the bicuculline model in which $GABA_A$ receptors are blocked by high concentrations of the antagonist. In support of this, nAChR was

reported to directly modulate immature CA3 excitatory synapses, irrespective of any effects on GABA release (31).

In the results indicated in this study no significant enhancement of EPSP amplitude was seen following DMPP application in the CA1 region. Application of DMPP enhanced glutamate afferent evoked fEPSP amplitude in the CA3 region of the hippocampus, but, no such effect within area CA1. This observation is consistent with studies reporting that activation of nAChR enhances glutamate release from CA3 pyramidal cells (10) but not from CA1 neurons (4, 6, 7, 15). Work performed by Alkondon *et al* (1997) showed that CNQX, a competitive glutamate receptor antagonist that inhibits fast glutamatergic transmission mediated by AMPA/Kainate receptors, failed in blocking nAChR-elicited PSCs in CA1 pyramidal cells, which indicated that nAChR activation is not linked to the release of glutamate in CA1 neurones (4). This finding is further supported by Jones *et al* (1997) and Frazier, Rollins *et al* (1998) who showed pyramidal cells in the area CA1 to be completely unresponsive to nicotinic receptor activation (15, 6). McQuiston and Madison (1999) also reported that only 2 out of 15 pyramidal cells in area CA1 responded to ACh application and that such responses were barely detectable and significantly smaller than equivalent nAChR mediated responses recorded in hippocampal interneurones (7). However, studies by Liu *et al* (2003) generally disagree with these findings reporting enhancement of excitatory synaptic transmission by activation of nAChRs on CA1 pyramidal cells, as well (32). This conflicting data is likely due to differences in the method and concentration of drug application, in the method of electrophysiology recordings and/or in the experimental conditions of the recording activity. Clearly however, further studies are required to establish the precise synaptic sites involved in the enhancement of glutamate transmission.

In spite of the conflicting data in the literature, the conclusion drawn from these data suggests that nAChR activation may regulate (potentiate) glutamatergic transmission at a subset of synapses. The apparent selective modulation of glutamatergic transmission by nAChRs mirrors the finding that muscarinic acetylcholine receptors (mAChRs) are reported to differentially suppress different excitatory pathways within the hippocampus (33). Such an action of nAChRs would be consistent with the previous modelling studies which predicted that the susceptibility of the hippocampus to generate epileptiform activity is proportional to the strength of glutamatergic connectivity in recurrent collateral synapses in CA3 region (24, 25) . The terminating of CA3 bursts depends on depletion of the releasable glutamate pool at these recurrent synapses, therefore, presynaptic factors controlling glutamate release at recurrent synapses regulate the probability and duration of synchronous discharges of the CA3 network (24). According to Vogt and Regehr (2001) acetylcholine directly modulate these synapses (14). Thus, it is possible that frequency potentiation mediated by nAChRs reflects the activation of presynaptic nAChRs that facilitate glutamate release which, in turn, forces the network into a higher frequency bursting models.

Irrespective of which regions of hippocampus is/are operating, the finding that nAChRs potentiate glutamatergic transmission in hippocampus raises the possibility that these receptors may be important regulators of synchronised neuronal activity. Whilst we hypothesize this, further effort is required to establish (a) whether this finding is reversible upon co-application of nAChRs selective antagonists to confirm the role of nicotinic receptors in modulating glutamatergic transmission and (b) whether increasing concentrations of DMPP may enhance glutamatergic transmission in a concentration dependent manner. Many classical pharmacological techniques (e.g., dose-response curves, tests for competitive and noncompetitive antagonisms) can be used to establish whether different nAChR subtypes impact on this cellular process. Furthermore, it is also necessary to establish the precise nature

of interaction among glutamatergic and cholinergic transmission in hippocampus.

Conclusion

In conclusion, this study shows that application of DMPP resulted in a sustained yet reversible enhancement of glutamate afferent evoked field EPSP amplitude in the CA3 region of the hippocampus. Whilst we can not rule out a possible postsynaptic sensitisation-type action on glutamatergic transmission we feel that this is unlikely. Instead, we hypothesise that activation of nAChRs by DMPP enhances glutamate release from presynaptic terminals, which in turn can strengthen recurrent excitatory connections in area CA3 and thus facilitate polysynaptic reverberations throughout the network. The observation that brain nAChRs regulate synchronised neuronal activity suggests that nAChRs represent a potential target in developing novel treatments for the control of pathological network conditions such as epilepsy.

Acknowledgments

This work was supported by Glasgow University, Glosgow, UK and Urmia University of Medical Sciences, Urmia, Iran. The authors declare that they have no conflict of interests.

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