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Research report

Postnatal development changes in excitatory synaptic activity in the rat locus coeruleus neurons

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ABSTRACT

Glutamatergic synapses are shown to mature during activity and development. In order to further explore how glutamate can change the excitability of noradrenergic neurons of locus coeruleus (LC) and to better understand the involvement of Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors complements across the LC, we investigated developmental changes in their activity during first postnatal weeks.

Spontaneous and evoked excitatory postsynaptic currents (sEPSC and eEPSCs) were recorded in neurons of LC slices from 7, 14 and 21 days old rats using the whole cell patch clamp method. Also, the AMPA/NMDA current ratio (A/N) was measured.

A pronounced AMPAR and NMDAR components mediated involvement in synaptic transmission were seen from the first postnatal week. Over this period of development, we have demonstrated that AMPA sEPSCs show an increase in frequency without major changes in their amplitude, while NMDA sEPSCs show an increase in frequency with a major change in amplitude. Neither the probability of release nor the AMPA/NMDA ratio was found to change significantly with age.

It is concluded that NMDAR activity as well as AMPAR activity may be involved in coerulear excitability and modulatory effect during postnatal development.

1. Introduction

During postnatal development, glutamatergic synapses undergo maturation and diversity of AMPA and NMDA receptors activity. In initial stages of development, some brain synapses comprise just NMDA receptors and the rapid insertion of AMPA receptors into these synapses is thought to underlie their maturation (Watt et al., 2000). In visual cortical synapses it has been shown that neural activity modulates the AMPA and NMDA components of EPSCs to sustain a steady ratio (Friedman et al., 2000; Watt et al., 2000). Recent studies have shown that there are significant modifications in glutamatergic neurotransmission from the birth until adulthood. Of especial notice is an alteration of the NMDA EPSC amplitude to AMPA EPSC ratio which reaches its maximum at second postnatal week and then declines until adulthood (Zhang et al., 2014).

The pontine nucleus locus coeruleus (LC) sends extensive noradrenergic projections throughout the widespread areas of central nervous system and contributes a modulatory role in the overall cognitive performance, vigilance, and learning and memory (Ishibashi et al., 2009; Ishimatsu and Williams, 1996; Masaki et al., 2004; Williams et al., 1984). Previous studies have shown that the excitability of LC neurons is regulated by excitatory synaptic inputs and in vivo application of glutamate receptor agonists can increase the firing frequency of LC neurons (Koga et al., 2005). So, to achieve the modulatory role, the glutamatergic innervations of the LC that primarily drives from nucleus paragigantocellularis (PGi) have probably to be finely tuned during postnatal development (Aston-Jones et al., 1991; Van Bockstaele et al., 1998), but the contribution of AMPA and NMDA receptors in LC function during development was not detected.

In glutamatergic synapses while AMPA receptors cause fast excitation, rise fast in hundred microseconds and decay in a few milliseconds, NMDA receptors show slow kinetics, make a much slower and longer-lasting current and they flux Ca^{2+} ions. So, the AMPA/NMDA ratio at a synapse will profoundly influence the time course and summation of synaptic currents (Malenka and Nicoll, 1999; Myme et al., 2003).

In this study we examined the coerulear glutamatergic synapse EPSCs during the initial three weeks of postnatal development and determined whether the ratio of AMPA and NMDA receptors are modulated in this period.

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2. Results

Fig. 1A exemplified traces of AMPA and NMDA sEPSCs, recorded at −80 and +40 mV in the presence of Bic + APV and Bic + CNQX, respectively in P14 rats.

Fig. 1B and C shows amplitude and frequency of AMPA sEPSCs and NMDA plotted versus postnatal age, respectively ($P<0.05$; recorded from 6 LC neurons of 5 rats).

Amplitude of NMDA sEPSCs in P14 and P21 rats was increased respecting to P7 ones, but AMPA sEPSCs amplitude did not show any significant variation (Fig. 1B). AMPA and NMDA sEPSCs frequency were increased significantly in P14 and P21 rats respecting to P7 ones (Fig. 1C). The probability of observing a NMDA receptor-mediated component in the sEPSC was largest during the second postnatal week. In Fig. 1D the frequency and amplitude ratio of AMPA/NMDA sEPSCs ratio for each cell is plotted against the postnatal weeks, which had no significant differences between the different postnatal ages.

Representative traces of AMPAR and NMDAR mediated eEPSCs have shown in Fig. 2 that were evoked by extracellular stimulation 50–100 μ lateral to the recorded cell at −80 mV and at +40 mV, respectively from P14 rats. These records were obtained in the presence of Bic + APV and Bic + CNQX respectively. Fig. 2B shows an increase in the peak amplitude of eEPSCs recorded from 6 LC neurons of 5 rats during the second and third weeks for NMDA and third week of age for AMPA currents compared to the first week ($P<0.05$; n=6). Average A/N ratios showed no significant difference for the amplitude (Fig. 2C).

AMPA and NMDA receptor kinetic changes over development during the first postnatal weeks. Fig. 3 shows the rise and decay slope of AMPA and NMDA EPSCs evoked by pericoerulear stimulation. AMPA rising slope did not show any significant change

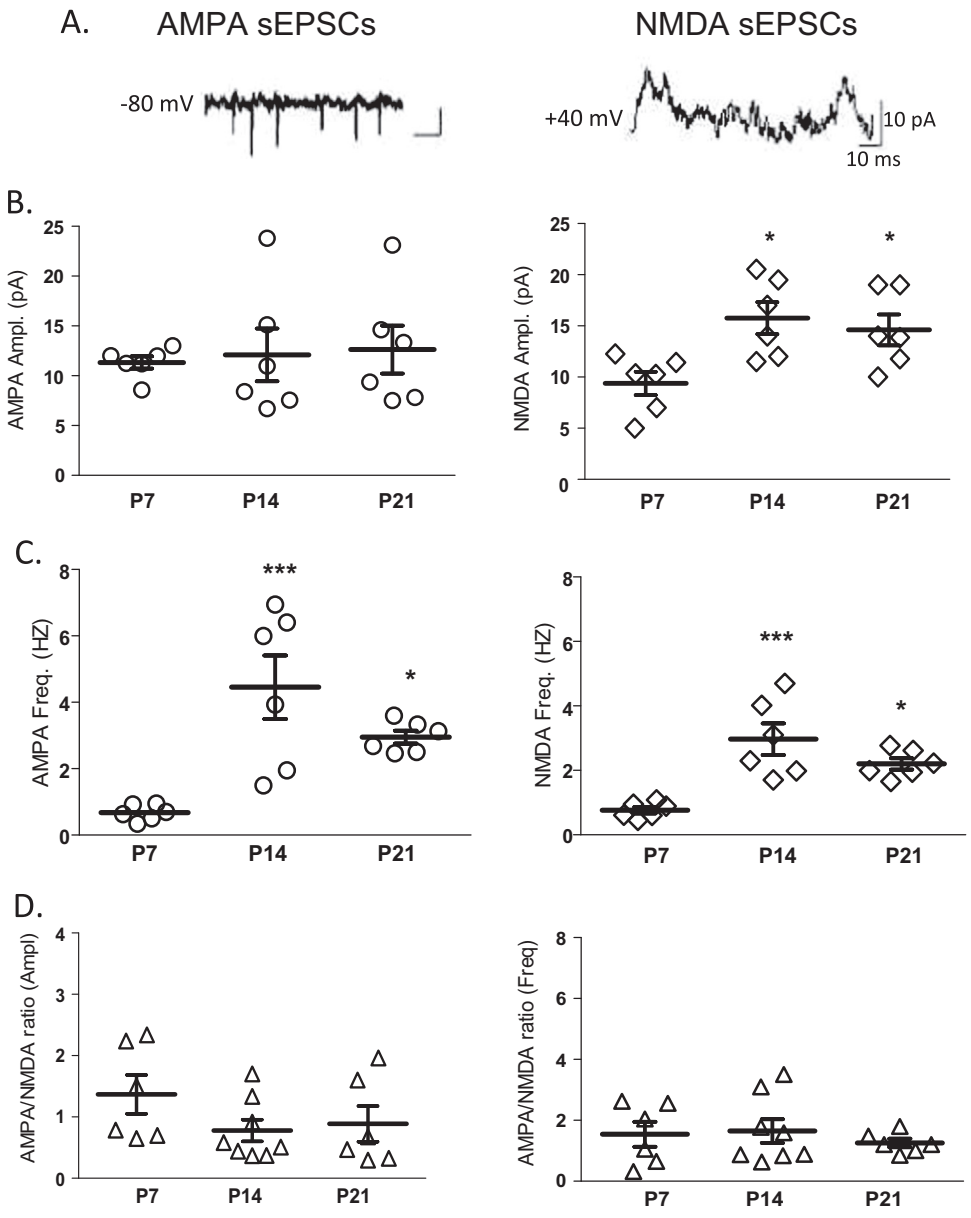

Fig. 1. AMPA and NMDA sEPSC amplitudes and frequencies in locus coeruleus neurons of P7, P14, and P21 rats. A, Sample sweeps illustrating AMPA sEPSCs recorded at −80 in the presence of Bic+APV (left trace) and NMDA sEPSCs recorded at +40 mV in the presence of Bic+ CNQX (right trace) in P14 rats. B, Amplitude (left plot) and frequency (right plot) of AMPA sEPSCs plotted versus postnatal age (* $P<0.05$). C, Amplitude (left plot) and frequency (right plot) of NMDA sEPSCs plotted versus postnatal age (*$P<0.05$;** $P<0.01$;***$P<0.005$). D, Graph of AMPA/NMDA ratios as a function of amplitude (left plot) and frequency (right plot) versus age ($P<0.05$). Average value for each postnatal day is represented by a horizontal line. All data are expressed as means ± SEM (n=6).