Postnatal development of perisomatic inhibition to pyramidal neurons in prefrontal cortex of mouse

Chor Hoon Poh

Disturbances in neural activity and imbalances between different neurotransmitters systems within the prefrontal cortex (PFC) have been associated with psychiatric diseases. Just as a balance in the excitatory and inhibitory neural network is important for normal brain functions, the specific time window in the construction of neural circuits is also mandatory for proper neurodevelopment. The aim of the present study was to examine the developmental changes of perisomatic inhibition of pyramidal neurons of ACC during the postnatal development of mice. In view of the key role of perisomatic inhibition we also studied the modulatory roles of (i) CCK; (ii) dopamine receptors.

In this study, our results revealed the 1st and 3rd postnatal week as the critical developmental phase in ACC of mice. There was a gradual increase from 1st to 3rd postnatal week and a decrease in the amplitude and frequency of inhibitory activity by the 4th week, both in sIPSCs and mIPSCs. mIPSCs recorded from pyramidal neurons also exhibited an age-dependent increasing sensitivity to TTX. In addition, kinetics analysis of events revealed a decrease in the decay time with respect to increasing postnatal age for both sIPSCs and mIPSCs. Blockade of D1-receptor by SCH 23390, a D1-receptor antagonist caused a decrease in both sIPSCs and mIPSCs frequency, whereas there was a bell-shaped response in the amplitude of sIPSCs. Interestingly, pyramidal neurons of ACC appear to be insensitive to CCK8 agonist up to 8 week of postnatal age.

A decrease in the inhibitory activity at 4th postnatal week may be a hallmark of network stabilization following synaptogenesis and may be accounted for by possible retraction of axons to 'refine' the circuit. TTX-insensitivity from 1st to 3rd week indicate that action potential-independent GABA release from presynaptic terminals may be the predominant form in providing spontaneous tonic GABAergic activity essential to drive the expression of receptors and establishment of functional synapses. The decrease in decay times of sIPSCs and mIPSCs events with increasing age suggests a developmental switch from α2-containing GABAA receptor subtype to α1-containing subtype. This switch may be important because of the faster efficacy of neurotransmission that is needed to accommodate the complexity of the growing neural network. In the ACC, enhancement of inhibitory transmission seems to be modulated by D1-receptor. It is postulated that dopaminergic neurons enhances inhibitory input to pyramidal cells (through both phasic and tonic release of DA) by exciting GABAergic interneurons through D1-receptor present to increase GABA release, which would dampen the synaptic activity of the postsynaptic pyramidal cell. Interestingly, the bell-shaped response could indicate possibility in the existence of another neurotransmitter system, likely serotonin, playing modulatory roles in ACC next to DA. The insensitivity of ACC neurons in response to CCK up to 8 weeks of postnatal age in mice might be because CCK receptors were not yet formed or expressed. Even though CCK results are inconclusive, it is believed that CCK does exert effects on the ACC neurons.

Psychiatric diseases are generally regarded as being developmental diseases in which disorders occur during development of the brain. By focusing on inhibitory transmission in normal neurodevelopment, we have gained a criterion of the normal inhibitory developmental pattern and the critical time window in the formation of network activity in the prefrontal cortex. This would be beneficial to identify a defect in neurodevelopment and the consequences that occur thereafter, making it easier for earlier possible intervention sites one could make in preventing or attenuating the symptoms implicated in psychiatric diseases. Most importantly, in the long term study of inhibitory transmission in the ACC, comparing data we obtained in this study with the pattern of inhibitory transmission observed in the conditional knockout mice (perhaps involving up- or downregulation in the gene expression of PV interneurons or susceptibility genes in psychiatric diseases) or using molecular tools to manipulate action potential-independent release (using protein kinase A or C inhibitors or botulinum toxin) at specific time points in postnatal life would be useful for our
understanding of the implications defects in development of perosomatic inhibition and its relevant circuits could have on psychiatric diseases. In doing so, our study could contribute another aspect to the wider picture that is needed in the attempts to correlate neurodevelopment to psychiatric diseases.