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Developmental synaptic plasticity at the thalamocortical input to barrel cortex: Mechanisms and roles

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The thalamocortical (TC) input to layer IV provides the major pathway for ascending sensory information to the mammalian sensory cortex. During development there is a dramatic refinement of this input that underlies the maturation of the topographical map in layer IV. Over the last 10 years our understanding of the mechanisms of the developmental and experience-driven changes in synaptic function at TC synapses has been greatly advanced. Here we describe these studies that point to a key role for NMDA receptor-dependent synaptic plasticity, a role for kainate receptors and for a rapid maturation in GABAergic inhibition. The expression mechanisms of some of the forms of neonatal synaptic plasticity are novel and, in combination with other mechanisms, produce a layer IV circuit that exhibits functional properties necessary for mature sensory processing.

Keywords: Glutamate; LTP; LTD; AMPA receptor; NMDA receptor; Kainate receptor; Critical period

Contents

Introduction

The facial vibrissae (whiskers) of rodents are somatotopically represented in the primary somatosensory cortex by cylindrical arrangements of neurons known as barrels (Woolsey and Van der Loos, 1970). Sensory information from the whiskers passes via the brain stem and thalamus to layer IV neurons in "barrel cortex" (Fig. 1A). Anatomical (Woolsey and Van der Loos, 1970) and electrophysiological (Welker, 1971) studies show that each whisker projects preferentially to a single barrel. In adult animals this preference is seen in electrophysiological recordings from layer IV as a short latency (5–10 ms) response to deflection of only the corresponding principle whisker mediated by activation of the thalamocortical (TC) input. Layer IV neurons also show responses to stimulation of non-principal whisker stimulation, so-called surround receptive field (SRF) responses, but unlike the principle whisker responses, these are thought to involve cortico-cortical connections (Armstrong-James and Callahan, 1991; Armstrong-James et al., 1991). This receptive field is, however, subject to experience-dependent plasticity: if all but one whisker is trimmed, short latency responses to deflection of the remaining whisker appear in other barrels. This plasticity in layer IV is most prominent if the whiskers are trimmed within the first postnatal week, although other forms of intracortical plasticity persist later in development (Diamond et al., 1993, 1994; Fox, 1992, 2002; Wallace and Fox, 1999). Thus the first postnatal week represents a period of enhanced plasticity in layer IV, similar to critical periods described for other forms of experience-dependent plasticity, for example in the visual system.

A slice preparation has been developed in which the TC afferents are preserved for *in vitro* electrophysiological studies (Figs. 1B–F). In this preparation electrical stimulation in the ventrobasal complex (VB) of the thalamus allows the study of monosynatically activated TC synapses (Agmon and Connors, 1991), something which has been possible for auditory (Cruikshank et al., 2002) and visual cortex (MacLean et al., 2006) only relatively recently. This preparation together with the ease of anatomically identifying the barrel field both histochemically (Woolsey and Van der Loos, 1970) and also in unstained

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slices (Agmon and Connors, 1991), and the well-defined mapping of whiskers to barrels, makes the barrel cortex a uniquely well-placed model for studying the synaptic mechanisms underling the development of the sensory map. Such studies have shown that a number of mechanisms are involved in mediating this development and refinement of the cortical map. NMDA receptor-dependent long-term plasticity occurs at the TC synapse only during the critical period for layer IV experience-dependent plasticity (Crair and Malenka, 1995) and results in a switch to fast AMPA receptor-mediated synaptic transmission from slow kainate receptor-mediated transmission (Bannister et al., 2005; Daw et al., 2006; Kidd and Isaac, 1999). At the same time TC projections refine to within individual barrels in a manner dependent on synaptic activity (Lu et al., 2006; Persico et al., 2001; Schlaggar and O'Leary, 1991) and cortical neurons migrate to the edge of the barrels whilst their dendrites become orientated towards the centre, a process that may also require activity (Inan et al., 2006; Iwasato et al., 2000).

Long-term potentiation (LTP) at TC synapses

LTP is a long-lasting and activity-dependent increase in synaptic strength (Bliss and Collingridge, 1993). A variety of stimulation protocols both artificial and pseudo-natural have been used that result in an increase in synaptic transmission in many brain areas (Malenka and Bear, 2004). Although the mechanisms

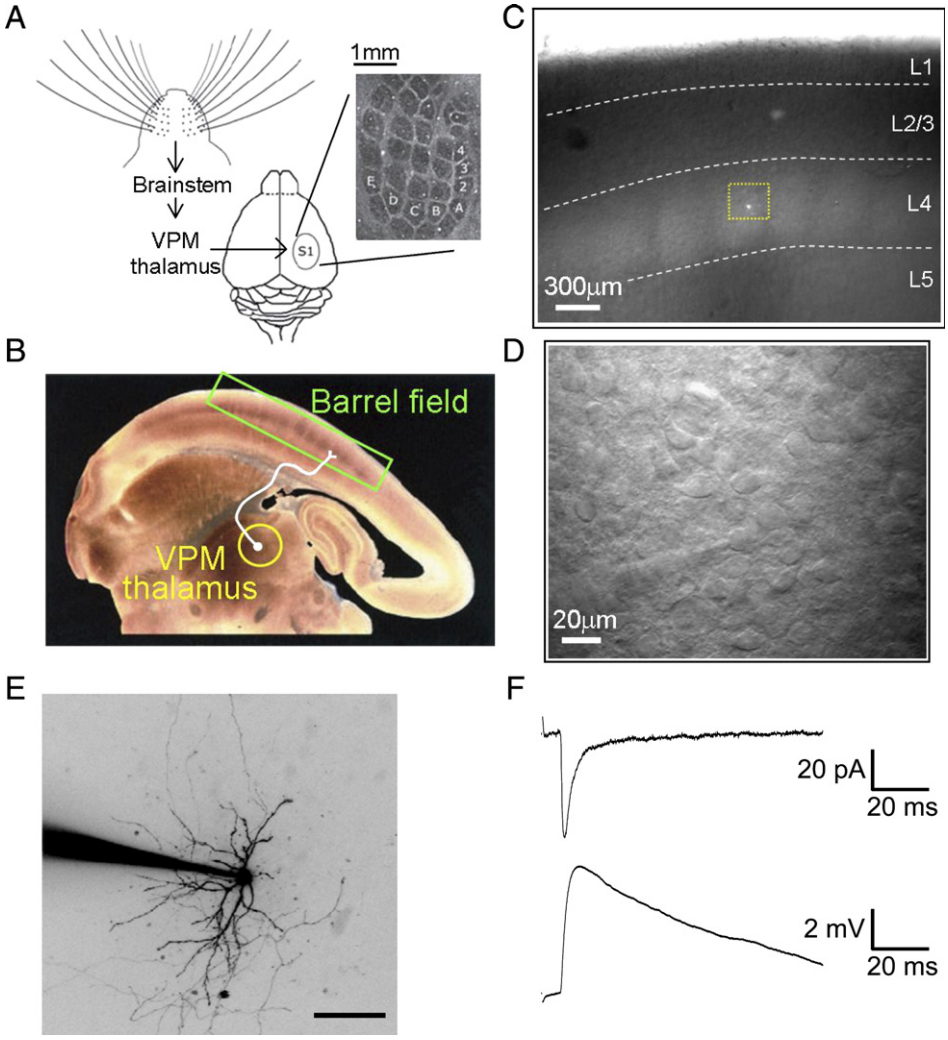

Fig. 1. Electrophysiological recordings from neurons in layer IV barrel cortex in the thalamocortical (TC) slice preparation. (A) Schematic of the afferent pathway from the whiskers to barrel cortex. Inset: cytochrome oxidase C-stained tangential section through layer IV of barrel cortex showing the distinctive cytoarchitecture. Reproduced from Feldman and Brecht (2005). (B) Cytochrome oxidase C-stained TC slice from 2-week-old rat. The ventroposteriomedial nucleus of thalamus (VPM) that receives ascending sensory input from the whiskers, and the barrel cortex are indicated. Reproduced from Petersen and Sakmann (2000). (C) Unstained TC slice from P5 mouse as it appears in recording chamber during an electrophysiology experiment. Highlighted by the yellow box is a stellate cell (SC) filled with the fluorescent dye Alexa-594 during a whole-cell patch-clamp recording (Daw, Ashby and Isaac, unpublished). (D) High power image of the region highlighted in C, showing a whole-cell recording from an SC (patch electrode can be seen as the out of focus shadow in bottom left hand corner). (E) 2-Photon image (flattened projection of Z-stack, contrast inverted for display) of an SC filled with Alexa-594 during patch clamp recording. (F) TC synaptic responses recorded during a whole-cell patch-clamp recording from an SC evoked by electrical stimulation of VPM thalamus. Top is an EPSC (voltage-clamp recording) and bottom EPSP (current clamp recording); responses collected in the same cell in response to the same stimulus (Daw, Ashby and Isaac, unpublished).