Review Article

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The first cortical circuits: Subplate neurons lead the way and shape cortical organization

https://doi.org/10.1515/nf-2018-0010

Abstract: The cerebral cortex is essential for our sensory experiences and conscious thought. Its neural connections, in particular sensory areas of the cerebral cortex, are shaped and sculpted by our early sensory experiences. Onset of these first sensory experiences of the world mark an important developmental event, enabling our worldy interactions to shape the makeup of our cerebral cortex. These long-lasting effects of early sensory experience are particularly striking in human communication, since early exposure to the mother's language is required to detect all nuances in the underlying sounds. Early interactions with the world are mediated by a key set of neurons, subplate neurons, which remain part of the developing cerebral cortex until most of them disappear at later stages of development. They play a crucial role in the developing mammalian brain. Here I review the circuitry and functional roles of cortical subplate neurons, focusing on their purpose in the development of primary sensory cortices.

Introduction

Our sensory experience is crucial to brain function, and whatever we experience early in life can end up shaping perception in adulthood. This effect of early experience is especially striking in the auditory system, which is essential for human communication. Early experience with language sculpts the auditory system such that sounds specific to certain languages can be detected. One crucial question is: at which age and in which part of the brain do sensory experiences elicit circuit changes to enable the perception of specific sounds? Studies of maternal voice suggest that prenatal experience plays a role in development of the auditory system. Since newborns already show a preference for maternal voice (DeCasper and Fifer, 1980; Mehler et al., 1988; Voegtline et al., 2013) the relevant processes are likely active from early stages in development. This review highlights organization of the fetal cortex and examines structures and circuits that underlie the development of sensory processing functions, in particular the processing of sound information.

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Prenatal sensory development

A large fraction of human cortical development occurs in the womb (Fig. 1A), even though the womb does attenuate sensory activation. While somatosensation (the sense of touch) can be active in utero, visual stimuli do not penetrate the womb and thus the retina will not easily be activated. By contrast, it has been well observed that human fetuses can respond to sounds before birth. In prenatal humans, auropalpebral reflexes (blink of the eye to loud sounds) emerge in the 20th gestational week (Birnholz and Benacerraf, 1983) (Fig. 1B), indicating that the inner ear is transducing sounds and that at least brainstem circuits involved in reflexive responses are functioning. However, because sounds are attenuated by the uterus, auditory thresholds are higher at these early developmental ages than after birth (Werner, 2007). Similar developmental progressions occur in other mammals, although some commonly used animal species (e. g. rodents and ferrets) are altricial, being born in a very immature state with closed eyes and ears. Thus, many developmental events occurring in utero in humans occur ex utero in these species and are thus readily studied (Fig. 1B). However, because eyes and ears are initially closed in these animals there also exists a period in which sensory transduction can occur, but where sensory inputs are attenuated.

The ability of the human fetus to respond to sounds raises the question of what stimuli impinge on the developing auditory system and what are the functional consequences of such stimulation. Both external sounds and maternal heartbeats can elicit fetal magnetoencephalographic (MEG) responses (Blum et al., 1985; Wakai et al., 1996; Eswaran et al., 2000; Lengle et al., 2001; Schleussner et al., 2001; Schneider et al., 2001; Zappasodi et al., 2001;

Figure 1

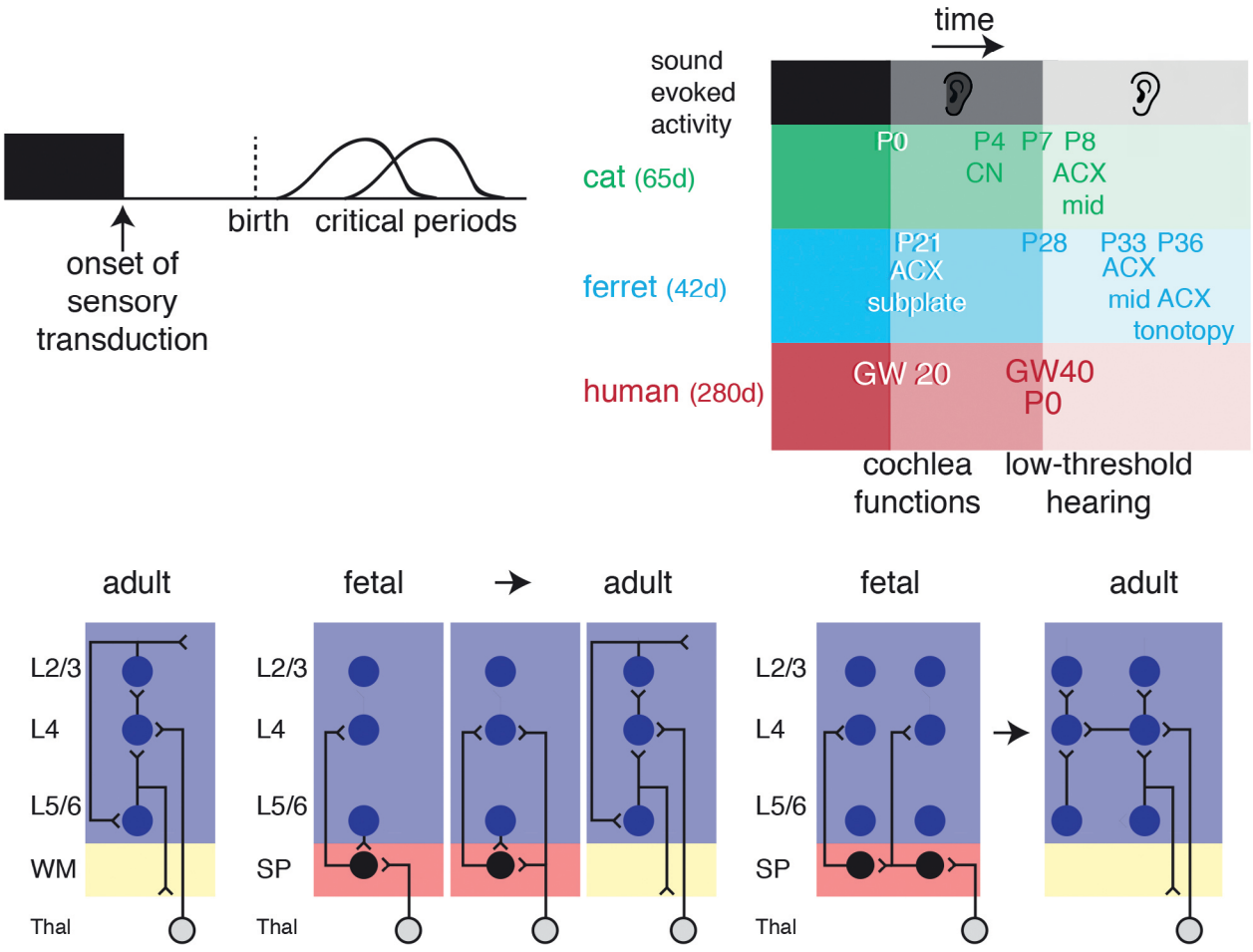

Figure 1: Changing circuits in the developing sensory cortex
A: Schematic of sensory development in humans. Sensory transduction can occur before birth. Critical periods, during which sensory experience can cause persistent alterations in sensory development have been identified postnatally. B: Schematic diagram of auditory development in three species. Gestation period indicated in brackets. Shading indicates amount of sensory information present. Black: Sensory transduction is absent. Dark gray: Sensory transduction is present but sound is attenuated by closed ears or the womb. Light gray: Sounds are not attenuated. P: postnatal day; GW: gestational week. ACX=Auditory cortex. C: Circuitry of adult sensory neocortex. WM=white matter; Thal=thalamus. D: Changing circuitry of developing sensory neocortex. E: Intra-SPN connection could precede and seed intra-L4 connections. CN=Cochlear nucleus.

Eswaran et al., 2002; Draganova et al., 2005; Porcaro et al., 2006). Even though auditory experience in a human fetus is attenuated by the womb, the preference for maternal voice in newborns (DeCasper and Fifer, 1980; Mehler et al., 1988; Voegtline et al., 2013) suggests that sounds can activate the human auditory system in utero, and that these sounds are processed in a complex manner supporting recognition of the mothers' voice.

While some motor responses seem reflexive, the selectivity of newborn infants for maternal voices is strong evidence to suggest that higher order processes are functioning. Since complex auditory processing is thought to occur in the auditory cortex (Nelken, 2004), early sensory experience might already act there. The mammalian cerebral cortex is a complex neural structure characterized by high interconnectivity and required for processing and consciously acting on sensory information. It is well known that sensory experience can shape connection from the thalamus to the cerebral cortex as well as the connections within the cerebral cortex. For example, depriving developing animals of sensory information in early life prevents maturation of connections from the thalamus to the cortex

and alters the pattern and function of intracortical connections (Sanes and Bao, 2009; Erzurumlu and Gaspar, 2012; Espinosa and Stryker, 2012).

Structural differences between the developing and adult cerebral cortex

When and where does sensory experience first interact with and shape the cerebral cortex? The adult cerebral cortex is a laminated structure with 6 layers. In sensory cortical areas, sensory information from the thalamus predominantly innervates the middle (granular) cortical layer (L4). From this input layer, information flows to the more superficial layers (L2/3) and to the deeper layers (L5/6) (Fig. 1C). Neurons from L2/3 and L5/6 project to intracortical or subcortical structures, respectively. In addition, neurons within each layer are also highly interconnected via intralaminar connections.

The developing cerebral cortex shares basic laminar topology with the adult cerebral cortex, however the cortical layers form gradually over development in an inside-out manner (in a structure termed *cortical plate*), hence the deepest layers develop first. One important difference is that the developing cortex contains additional neurons located in the area where white matter will appear (Fig. 1D). These are called subplate neurons (SPNs); they comprise the earliest generated and maturing population of neurons in the mammalian neocortex (Krmpotic-Nemanic et al., 1979; Kostovic and Rakic, 1980; Kanold and Luhmann, 2010). In human auditory cortex, SPN neurons are distinguishable at 12–13.5 weeks (Krmpotic-Nemanic et al., 1979). During development, a large fraction of SPNs disappear, while some SPNs are thought to remain as a subpopulation of deep cortical neurons, layer 6b (L6b) (Kanold and Luhmann, 2010; Marx et al., 2015; Hoerder-Suabedissen et al., 2018). The functional role of L6b neurons in adults is not well understood, but because L6b neurons are modulated by neuropeptides, such as hypocretin, they might play a role in controlling wakefulness (Bayer et al., 2004; Case and Broberger, 2017; Case et al., 2017). It is possible that a fraction of SPNs serve a similar role in development.

SPNs are diverse, which might indicate different functional roles for the different SPN classes. SPNs can be classified into subpopulations based on their dendritic architecture or gene expression profiles (Kanold and Luhmann, 2010). Molecular analysis of SPNs in rodents and humans has revealed a panoply of subplate-specific markers, such as Connective Tissue Growth Factor (CTGF), Complexin3 (Cplx3), Nurr1 etc., suggesting the existence of molecularly-defined SPN populations (Hoerder-Suabedissen et al., 2009; Belgard et al., 2011; Hoerder-Suabedissen and Molnar, 2013; Bakken et al., 2016; Viswanathan et al., 2012, 2017; Lein et al., 2017). Furthermore, molecular profiling has enabled the study of subplate evolution, which has already identified subpopulations that are conserved across species, e. g., from birds to mammals, and other populations that seem to be specific to mammalian neocortex (Montiel et al., 2011; Wang et al., 2011; Molnar et al., 2014). Therefore, the study of how SPN neurons differ across species might hold clues to the evolution of the human neocortex, because SPNs seem to be overrepresented in species with more complex cortical organization (Kostovic and Rakic, 1990; Kanold and Luhmann, 2010). Unfortunately, associations between molecular markers, morphological, and functional SPN types remain unclear.

Subplate neurons provide an early relay of thalamic information and represent an early integrative hub

Important clues to the functional role of SPNs are given by the source of their synaptic inputs as well as by their outputs. From the earliest studies of SPNs it was clear that they were present in primary sensory cortices at times when thalamic axons entered the white matter. From these observations, it was hypothesized that SPNs serve as a transient target and waiting compartment (Kostovic and Rakic, 1990; Ghosh and Shatz, 1992b; Hevner, 2000; Kostovic and Judas, 2002). Physiological brain slice studies confirmed that SPNs in all primary sensory areas received excitatory thalamic inputs (Friauf et al., 1990; Higashi et al., 2002; Zhao et al., 2009) (Fig. 1D).

SPNs can have complex dendritic trees, suggesting that they receive an extensive set of synaptic inputs (Hanganu et al., 2002; Zhao et al., 2009; Kanold and Luhmann, 2010; Liao and Lee, 2012). As mentioned above, SPNs receive thalamic inputs. However, at later developmental ages they also receive excitatory and inhibitory inputs from the developing cortical plate, in particular from the future thalamocortical recipient layer L4 and the deeper layers L5/6, as well as from within the subplate (Viswanathan et al., 2012; Meng et al., 2014) (Fig. 1D).

Thus, SPNs integrate ascending information with intrinsic cortical activity.

Having identified their main inputs, the next clue to SPN function was provided by identifying their synaptic targets. Brain slice experiments in rodents showed that SPNs innervate L4 before thalamic axons activate L4 (Zhao et al., 2009; Deng et al., 2017) (Fig. 1D). This SPN to L4 projection is excitatory and targets both excitatory and inhibitory L4 neurons. Thus, SPN activity can change the balance of activity in L4.

Taken together, these identified circuits indicate that early thalamic activity is relayed to the future thalamic input layer, L4, via an obligatory relay in the subplate. This relay action can be observed in young brain slices. Subplate responds to thalamic afferents with short latency, while L4 responses have longer latency (Friauf and Shatz, 1991; Barkat et al., 2011). This circuit topology highlights the essential role of SPNs in relaying early thalamic inputs to L4 (Fig. 1D), enabling SPNs to influence the developing cortical architecture. Computational analysis has shown that SPNs can induce activity correlations between thalamic terminals and their future targets in L4 and thereby promote strengthening of thalamus-L4 synapses by forming a "teacher circuit" (Kanold and Shatz, 2006; Kanold, 2009; Butts and Kanold, 2010). This instructive role of SPNs might also generalize and apply to intracortical circuits. For example, SPNs connect to each other, and thus their activity might cause correlated activity in spatially distinct populations of L4 neurons. Such correlations might contribute to formation of spatially patterned connections within L4 (Fig. 1E).

Besides projecting to L4 and other targets in the developing cortical plate, SPNs have also been shown to connect to subcortical structures such as the thalamus (McConnell et al., 1989, 1994; Viswanathan et al., 2017; Hoerder-Suabedissen et al., 2018). As a result, SPNs sit at the nexus between immature ascending and descending thalamocortical and corticothalamic pathways.

Subplate neurons are the first cortical neurons to exhibit sensory responses and nascent topographic organization

Given that SPNs in sensory cortices receive thalamic inputs, it follows that peripheral sensory stimulation might activate them, because peripheral receptors can function before onset of thalamic transmission to L4. The opening of eyes and ears in altricial animals, such as mice, roughly coincides with the onset of thalamic transmission to L4 (Barkat et al., 2011). Although it has commonly been assumed that before this time point no sensory activation of cortex is present, direct and indirect evidence suggest otherwise. Peripheral receptors, like retinal photoreceptors or cochlear hair cells, can function at earlier ages, and thus sensory evoked activity could be present along ascending sensory pathways. Recordings in ferrets and mice, born with closed eyes and ears, showed that cells in the visual pathway can respond to visual stimuli before eye opening (Krug et al., 2001; Akerman et al., 2002; Tian and Copenhagen, 2003; Akerman et al., 2004; Chen et al., 2009). Recent electrophysiological studies of the ferret auditory system indicated that the auditory cortex can respond to sound ~10 days before ear opening (Wess et al., 2017) (Fig. 1B). In these immature animals, sound-evoked local field potentials (LFPs) were present in both the future thalamocortical recipient layer, L4, as well as in subplate. Oscillatory LFP activity in response to whisker stimulation is also present in the subplate of the somatosensory cortex in neonatal rodents (Yang et al., 2009). Since LFPs reflect bulk electrical activity, these signals contain both neuronal spiking activity as well as synaptically-evoked potentials. To identify which population of neurons underlies this early activity, laminar recordings of single-unit activity (i. e. extracellular recorded spikes that can be assigned to a single neuron) were performed. These recordings revealed that the earliest responses originated from SPNs, and that responses in L4 emerged at later ages (Wess et al., 2017) (Fig. 2A). Furthermore, at ages during which responses were present in both subplate and L4, SPNs responded at shorter latencies, indicating that sound information reached L4 via SPNs; this is consistent with the SPN to L4 projections at early ages (Fig. 1D, 2B). These experiments indicate that sensory information is present in the cerebral cortex at much earlier ages than previously assumed and that the earliest active neurons are located in the subplate and not in L4. These results show that at least in the auditory system it is likely that sensory information is present in the sensory cortex shortly after the sensory end organs are capable of sensory transduction.

One hallmark of sensory cortices is their topographic organization: stimulus features, such as sound frequency, are mapped out on populations of neurons such that neighboring populations respond to similar features – with the overall stimulus preference varying smoothly across the cortex. The existence of early sound-evoked activity raised the question of whether early responses also showed topographic organization. LFP recordings

Figure 2

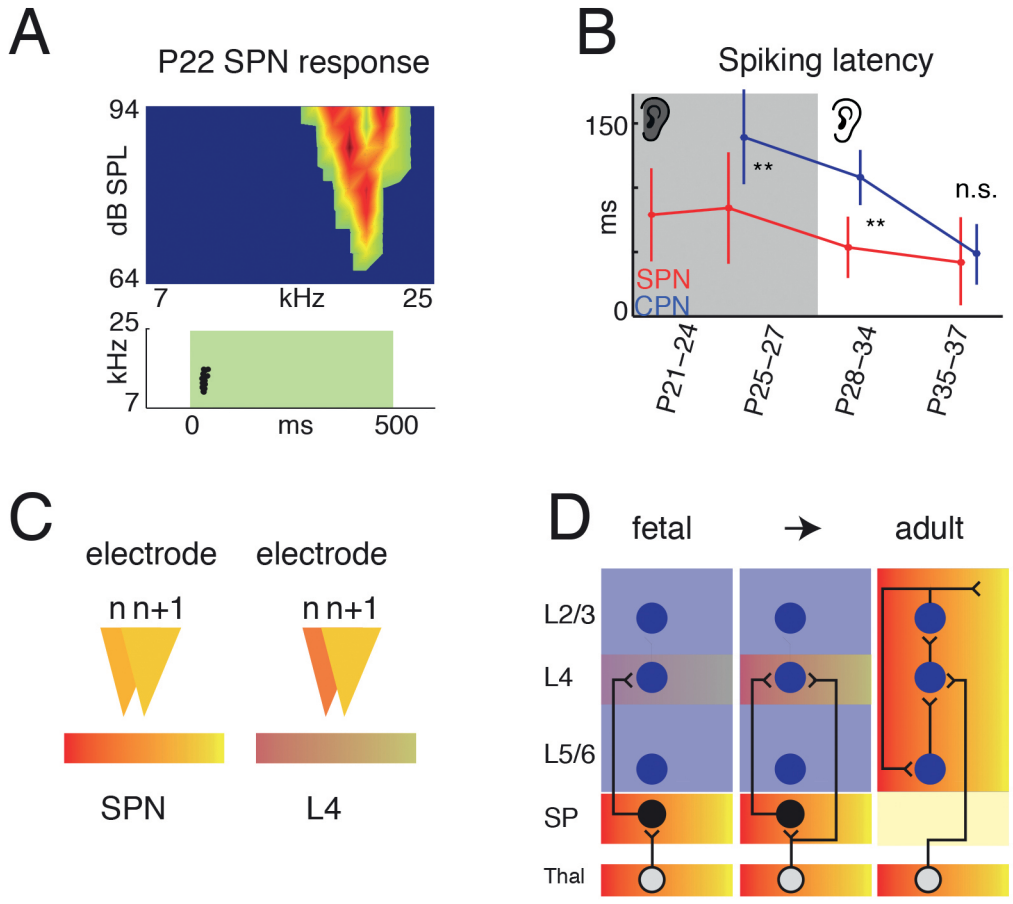

Figure 2: Early auditory responses in subplate
A: Example of a sound-responsive SPN. Shown are spiking rates (color) in response to tones of particular loudness. Note that this neuron is selectively responding to mid-frequency tones. Adapted from Wess et al. 2017. B: Latency of sound-evoked activity is shorter in SPN than in mid cortical plate neurons (CPN). Adapted from Wess et al. 2017. C: Cartoon illustrating the difference in frequency selectivity of LFP activity on neighboring electrodes. Colors represent different sound frequencies (Red: low tone frequency Yellow:high tone frequency). A higher local tuning similarity is present in subplate than L4. D: Hypothesized sequential development of tonotopy in cortical columns. Subplate is topographically organized at early ages. SP inputs to L4 establish frequency selectivity and promote the establishment of thalamic axon connections of the same frequency band to L4. Thus, L4 neurons will start to show an orderly progression of frequency preferences across columns.

using multi-electrode arrays demonstrated that neighboring electrodes in the subplate showed similar frequency preference, while neighboring electrodes in L4 showed less similarity (Fig. 2C). In addition, stimulus preference similarities were larger for closer electrodes, indicating that subplate might contain topographic maps of stimulus preference. These findings suggest that the topographic organization of the sensory cortex might be sketched out within the subplate (Wess et al., 2017) and transferred to L4 via the "teacher-circuit" (Fig. 2D).

Subplate damage and dysfunction are implicated in neuro-developmental disorders

Because SPNs are the earliest cortical neurons to mature, they are also the first to be susceptible to injury. Furthermore, researchers have suggested that SPN dysfunction plays a role in multiple neurodevelopmental disorders such as autism spectrum disorders (ASDs), cerebral palsy, and schizophrenia. To directly investigate the consequences of early SPN damage, SPN lesion studies have been performed in animal models. Such studies used ex-

citotoxic lesions via focal injections of kainic acid (Ghosh et al., 1990; Ghosh and Shatz, 1992a, 1993, 1994; Lein et al., 1999; Kanold et al., 2003; Kanold and Shatz, 2006) or targeted immuno-ablations (Kanold et al., 2003; Kanold and Shatz, 2006; Tolner et al., 2012) to remove SPNs in early development. Lesioning in very early development, at time points before thalamic axons have reached L4, showed that SPNs are required for normal ingrowth of thalamic axons to their target in L4 (Ghosh et al., 1990). Lesioning at a slightly older age, when thalamic axons have entered L4 but before these connections had matured, prevented the anatomical patterning and functional maturation of thalamocortical connections (Ghosh and Shatz, 1992a, 1993, 1994; Kanold et al., 2003; Tolner et al., 2012) as well as intracortical inhibition (Kanold and Shatz, 2006). Taken together, these animal studies showed that loss of SPNs prevents essential steps of cortical development from taking place, and that these neurons play a key role in promoting normal cortical development. Moreover, the multitude of lesioning effects across development suggests that SPNs play critical roles throughout.

Additional evidence for a role of SPNs in neurodevelopmental disorders arose from studies showing that hypoxic insults to the developing human fetus can result in damage to the subplate region (Kostovic et al., 1989; McQuillen and Ferriero, 2005). Further animal studies conclusively showed that neonatal hypoxic-ischemic injuries can cause loss of SPNs (McQuillen et al., 2003; Mikhailova et al., 2017), alter their morphology (McClendon et al., 2017), and lead to altered excitatory and inhibitory cortical circuits impinging on SPNs (Sheikh et al., 2018).

SPNs have also been implicated in autism spectrum disorders. Histological studies on human postmortem tissue from autism patients shows an altered boundary between L6 and white matter (Avino and Hutsler, 2010) as well altered neural cell number and patchy subplate gene expression changes (Courchesne et al., 2011; Stoner et al., 2014). Furthermore, exposure to valproate acid (VPA) during pregnancy results in enhanced risk of autism in humans and rodents (Roullet et al., 2013; Nicolini and Fahnestock, 2018) and rodent studies have shown that such neonatal exposure alters circuits to developing SPNs (Nagode et al., 2017).

Collectively, these studies show that SPNs are a common target in multiple animal models of neurodevelopmental disorders. Since SPNs influence the development of cortical neurons, altered subplate circuits likely give rise to altered cortical circuits and cortical function. It is possible that SPNs are also disrupted in other conditions. Further studies of SPNs in a variety of conditions are needed. The recent availability of molecular markers should enable these studies.

Subplate neuron activity can be modulated: potential effects of maternal exposure to drugs and pharmaceuticals

Excitatory and inhibitory inputs are not the only inputs to SPNs. Histological and brain slice studies have shown that SPNs are targeted by many neuromodulatory systems that can function in the developing brain. For example, SPNs can be modulated by acetylcholine (ACh) or serotonin (Hanganu and Luhmann, 2004; Dupont et al., 2006; Hanganu et al., 2009; Liao and Lee, 2011, 2014). Furthermore, SPNs label for a variety of other neuropeptides such as substance P, neuropeptide Y (NPY) etc. (Chun and Shatz, 1989; Antonini and Shatz, 1990; Kanold and Luhmann, 2010). In addition, SPNs that persist as L6b neurons are modulated by neuropeptides (Bayer et al., 2004; Case and Broberger, 2017; Case et al., 2017) suggesting that these neuropeptides might also influence SPNs at earlier ages. Therefore, fetal exposure to agonists or modulators of these signaling systems – such as maternal consumption of alcohol or drugs of abuse – might alter activity of SPNs directly via acting on SPN receptors. It has been noted that fetal drug exposure could lead to altered development of cortical circuits (Thompson et al., 2009). Altered SPN activity and function could underlie some of these developmental effects. Similarly, maternal stress or inflammation (Estes and McAllister, 2016) can potentially alter SPN function. However, to date none of these possibilities have been explored.

Open questions

SPNs are known to constitute a key neuronal population in early development, but many questions remain. In sensory systems, these neurons provide an early sketch of future cortical organization. However, the role of SPNs in other cortical regions has not been investigated. Many advances have been made in understanding SPN circuits and function, but most of these studies have been performed in rodents. Given that SPNs are more numerous in species with more complex brains, e. g. in humans, studies in other species are needed. Finally, SPNs are in a prime

position to be modulated by a variety of substances that cross the placenta, but evidence of such effects on SPN activity is lacking.

Acknowledgements: This work was supported by NIH RO1DC009607 (POK). The author would like to thank all past and current members of the laboratory for their invaluable contributions, Zara Kanold-Tso for comments on the manuscript, and Dr. Werner Kilb for help with editing and translation.

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