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CNS consequences of perinatal peripheral injuries

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The neonatal brain is a highly vulnerable organ. Developing neural circuits, during their major phase of construction, are highly susceptible to harmful conditions both from within and outside the body. Numerous intrinsically programmed molecular cues guide nerve cells and their processes to form highly specific synaptic connections and circuits in the brain. Neural activity plays a major role in refinement of these circuits and consolidation of synaptic relations. During the initial scaffolding and construction of these connections, the brain is highly sensitive to deleterious external conditions.

Effects of early brain damage on the development, organization and function of the nervous system, and ultimately behavior, have been documented extensively. However, relatively little attention has been devoted either to how and/or to which extent central neural circuits are modified following deleterious conditions that occur outside the central nervous system (CNS). This special issue of *Experimental Neurology* on *CNS consequences of perinatal peripheral injuries* features research and review articles that shed light on the effects of early peripheral injury or insult on brain organization and the current views on therapeutic approaches.

In contrast to a wide array of studies on sensory deprivation, critical periods, and brain plasticity, CNS consequences of neonatal peripheral nerve damage have not received much attention. Injuries to the peripheral sensory nerves during birth, such as brachial nerve palsy, are not rare. Accidental injuries to the peripheral nerves are also common in neonates and children. Most clinical and preclinical studies in neonatal peripheral nerve damage have focused on repair strategies and mechanisms of regeneration of peripheral nerves following injury. While damaged nerves can be repaired with significant functional recovery, it is not known to what extent the CNS circuits that receive inputs from these nerves undergo remodeling or synaptic plasticity. In “*Neonatal sensory nerve injury-induced synaptic plasticity in the trigeminal principal sensory nucleus*,” Lo and Erzurumlu focus on and review CNS consequences of neonatal peripheral nerve damage. The authors primarily evaluate the effects of neonatal infraorbital nerve damage in trigeminal CNS circuits in neonatal rodents, also discussing mechanisms of glial reactivity-induced synaptic plasticity following sensory nerve damage.

Not just peripheral nerve damage, but also tissue injury in early life can lead to dramatic changes in the organization and function of the somatosensory circuits, in particular the central pain matrix. Tissue injury resulting from a wide variety of causes ranging from major surgeries to simple blood collection by heel lancing in neonates and preterm babies can alter sensitivities and threshold for nociception in later life. In “*Persistent changes in peripheral*

and spinal nociceptive processing after early tissue injury,” Walker et al., review the clinical studies in neonates and children that have undergone early tissue injury and experimental studies in animal models that provided evidence that early tissue injury leads to persistent alterations in spinal and upstream nociceptive circuits. Preclinical studies offer insights into the mechanisms underlying organization and tuning of nociceptive circuits, both in the dorsal root ganglia and in the spinal cord in response to early tissue injury. Sensory neurons in the dorsal root ganglia or spinal nociceptive neurons are often sensitized to inflammatory stimuli or skin incision by changes in the function of receptor channels, intrinsic membrane properties and selective consolidation or elimination of excitatory, and inhibitory synaptic connections. Recent studies underscore the complexity of nociceptive signal processing in neonates by revealing contributions from the immune system through microglia.

Preterm infants spend a considerable time in the Neonatal Intensive Care Unit (NICU) and often do not receive anesthesia during various procedures to which they are subjected. Unalleviated pain and stress affects their pain sensitivity and incidences of neuropsychiatric disorders later in life. In their review “*The long-term impact of early life pain on adult anxiety and stress: Historical perspectives, the clinic and empirical evidence*,” Victoria and Murphy focus on early postnatal perturbations and stress, anxiety and pain perception in later life. They evaluate studies using a rodent model of early life pain and how neonatal inflammatory pain blunts responses to stress- and painful stimuli in adult life. Dysregulation of the hypothalamic pituitary adrenal axis through changes in central endogenous opioid tone is discussed. Neonatal inflammatory injury has pronounced effects on adult anxiety- and stress-related responses through wiring of the neural circuits, and the hypothalamic endocrine control systems. These studies bring significant insight to underlying mechanisms and potential preventive measures to alleviate perinatal pain in the NICU.

The two experimental contributions, included in this section, exemplify the effects of perinatal stress and hypoxic ischemia in perinatal animals on wiring and function of brain circuits. In “*Gender- and anxiety level-dependent effects of perinatal stress exposure on medial prefrontal cortex*,” Soztutar et al., examine the morphological features of the medial prefrontal cortex (mPFC) in rats that have been subjected to perinatal stress. They report that under stressful conditions, both male and female rats that have undergone prenatal stress show higher levels of neuronal activation as assessed with activity-dependent immediate early gene expression. They further see anxiety level- and sex-dependent reduction in the dendritic complexity and spine density of mPFC pyramidal neurons, particularly in neonatally stressed males.

Hypoxic ischemia (HI) of the brain in near-term infants is a major neurological problem, which often leads to mortality. In both preclinical and clinical studies, gender-related differential vulnerabilities have been noted. In the second research paper, “*Sex differences in cell genesis, hippocampal volume and behavioral outcomes in a rat model of neonatal hypoxia ischemia*,” Waddell et al., investigate gender differences on hippocampal cell genesis following neonatal HI in rats and assess the therapeutic effects of estradiol treatment, which has been used as a neuroprotectant in adult models of stroke. Their findings indicate that neonatal HI results in increased neurogenesis in both sexes in the long term. Behavioral assays that are largely specific for hippocampal function revealed differential

impairment between males and females and estradiol treatment improved behavioral performance but did not affect neurogenesis.

Developing mammals respond to nociceptive stimuli from embryonic ages. However neuropathic pain does not develop until adolescence. Fitzgerald and McKelvey review the immediate and long-term changes in spinal nociceptive circuits in response to nerve injury at different developmental time periods (*"Nerve injury and neuropathic pain - a question of age"*). There is mounting evidence, which indicates that age-dependent development of neuropathic pain is related to the maturation of neuroimmune regulation of pain circuitry. Late emergence of neuropathic pain following nerve injury is triggered by emergence of rapid pro-inflammatory response that leads to the sensitization of nociceptive spinal neurons, increased microglial activation, and release of pro-inflammatory cytokines.

This modest collection of review and research articles underscores the sensitive periods in development of the mammalian CNS. Peripheral nerve injuries, tissue damage, stress conditions can lead to significant cellular and molecular alterations in the brain that emerge as altered function later in life.