understanding of the neural circuitry involved and the range of spontaneous recoveries under different injury conditions. To address these issues, we have been investigating the spinal neural circuitry related to diaphragm function and respiratory changes following cervical SCI above or within the phrenic motoneuron (PhMN) pool. Neuroanatomical findings have demonstrated the presence of a population of spinal prephrenic interneurons (PINs), some of which receive descending projections from brain stem regions (VRC) subserving inspiratory drive to PhMNs. Correlative extracellular electrophysiological data suggest some PINs exhibit activity in phase with PhMNs and are responsive to hypoxic challenge in synchrony with elevated PhMN activity. These data support the possibility that PINs may play a role in some aspects of spontaneous recovery of ipsilateral PhMN function following a C2 hemisection lesion (C2Hx). To date, such neuroplasticity has been thought to be mediated entirely by uninjured, contralateral VRC fibers. Although there is a recovery of ipsilateral hemidiaphragm activity following C2Hx, prior findings suggest that ventilatory improvement was modest. Diaphragm electromyography (EMG) recordings 12 weeks post-C2Hx also revealed little progressive change beyond initial recovery, and anterograde tracing of VRC projections showed reduced innervation of ipsilateral PhMNs. To obtain a further measure of respiratory drive to these neurons, experiments were performed in which ipsilateral (left) and contralateral (right) diaphragm EMG activity was recorded following left or right phrenicotomies. Transection of the ipsilateral phrenic nerve resulted in a silencing of left diaphragm activity, whereas a compensatory increase in EMG response was seen contralaterally. Contralateral phrenicotomy silenced the right hemidiaphragm; however, only a minimal change in left diaphragm EMG recordings was observed. Absence of a significant ipsilateral response suggests that ventilation in the C2Hx rat is more reflective of compensatory rather than restorative neuroplasticity. We next explored to what extent respiratory function is affected after a clinically more representative contusion injury at the level (C3/4) of the PhMN pool. Plethysmographic measurements of breathing frequency and tidal volume were obtained under baseline room air conditions and during CO_2 (hypercapnic) challenge. Terminal recordings of diaphragm activity also were obtained. Both physiological measures revealed a progressive loss in the capacity to increase respiratory drive in response to hypercapnia. These studies reveal differential degrees of neuroplasticity relative to predominantly white matter (C2Hx) and combined white and gray matter (contusion) damage.

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Possible Involvement of Neurogenesis in Male Rat Mating Behavior

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Adult neurogenesis occurs in the dentate gyrus of hippocampus and subventricular zone (SVZ). Deficit of hippocampal neurogenesis brings impairment of spatial learning and memory, which suggests the physiological role of new born neurons in memory formation. In contrast, functional significance of new neurons born in SVZ remains elusive. Recent studies showed that neurogenesis in the SVZ is increased by pheromone exposure from the opposite sex and neurogenesis is essential for normal mating behavior of female mice. These results suggest that SVZ-derived new neurons may take part in reproductive function. The current study aimed at exploring the relationship between adult neurogenesis and male sexual behavior. Adult male Sprague-Dawley rats were treated with corticosterone and/or paroxetine (an antidepressant) for 2 weeks. These two drugs were shown to suppress and promote neurogenesis, respectively. Mating behavior was assessed after the treatment, and bromodeoxyuridine immunohistochemistry was used to identify new cells. Neural circuit activation of the mating-related pathway was assessed by c-fos immunostaining. To further confirm necessity of neurogenesis in male mating behavior, inhibition of neurogenesis was performed by intracerebroventricular infusion of cytostatic cytosine arabinose (Ara-c) and sexual behavior test was carried out. From cell quantification and mating behavior test, corticosterone treatment inhibited neurogenesis in the olfactory epithelium and SVZ, and simultaneously an inhibited sexual performance was found. Conversely, paroxetine treatment increased newborn neurons and enhanced the sexual performance in corticosterone-treated animals. When Ara-c was used to suppress neurogenesis, the sexual performance was suppressed. In addition, a decrease in cell proliferation was associated with a decreased level of c-fos expression in regions related to mating, including medial amygdala, bed nucleus of stria terminalis, and medial preoptic areas. Taken together, the results suggest that neurogenesis plays a role in male reproductive behavior in rodents. Alteration of neurogenesis rate may be a potential treatment option for sexual dysfunction.

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LPS-Induced Inflammation Exacerbates Phospho-Tau Pathology in rTg4510 Mice

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Inflammation and microglial arguably contribute to Alzheimer's disease (AD) pathology. Evidence shows that pathological hallmarks, notably amyloid-beta (Aβ) and hyperphosphorylation of tau activate microglia. However, it is less well understood how certain inflammatory events modulate Aβ and tau pathology. These studies were designed to elucidate the role of acute inflammation and its effects on tau pathology. We used transgenic rTg4510 mice, which express the P301L mutation (4R0N TauP301L) and initiate tau pathology between 3 and 5 months of age. We injected either saline or lipopolysaccharide (LPS; 5 μg per site; two sites) into the right frontal cortex and hippocampus of 5-month-old mice rTg4510 or nontransgenic littermate mice. One week postinjection, brains were harvested and analyzed by immunohistochemistry for markers of microglial activation and phospho-tau species using unbiased image analysis. Microglial activation was measured by induction of CD45 (general activation marker) and alternative activation markers YM1 and arginase. LPS induced significant activation of CD45 and arginase activation. YM1 was further exaggerated in transgenic mice treated with LPS. Expression of phospho-tau Ser199/202 and Ser396 was observed in tau-laden area of transgenic mice only and increased in mice that received LPS compared to saline injections. However, mature tangles (silver positive) remained unaffected by LPS administration. These data suggest that inflammatory stimuli can facilitate tau pathology and that tau impacts the certain alternative activation markers. Coupled with prior results demonstrating clearance of Aβ by similar LPS injections, these results suggest that inflammation may have opposite effects on amyloid and tau pathology, possibly explaining the failures (to date) of anti-inflammatory therapies in AD patients.

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