PERSPECTIVES

Chronic pain and adult hippocampal neurogenesis: translational implications from preclinical studies

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Abstract: Adult hippocampal neurogenesis (ahNG) occurs in the human brain. Adult generated neurons have been proposed to functionally contribute to relevant hippocampal functions such as learning and memory, mood regulation, and stress response. Learning, environmental enrichment, and physical exercise exert positive effects on ahNG. In parallel, these proneurogenic stimuli have been shown to ameliorate cognitive performance and/or depressive-like behavior in animal models. Conversely, aging, social isolation, and chronic stress exert negative effects on ahNG. Interestingly, reduction of hippocampal neurogenesis is suggested to potentially contribute to cognitive decline and mood alterations associated with aging and several neuropsychiatric disorders. Clinical observation demonstrates that patients affected by chronic pain often exhibit increased anxiety and depression, impaired cognitive flexibility, and memory capacities. As of today, our understanding of the molecular and cellular events that may underlie the comorbidity of chronic pain, depression, and cognitive impairment is limited. Herein we review recent preclinical data suggesting that chronic pain may induce profound changes in hippocampal plasticity, including reduced ahNG. We discuss the possibility that deregulated hippocampal neurogenesis in chronic pain may, at least in part, contribute to cognitive and mood alterations. Based on this hypothesis, the mechanisms underlying chronic pain-associated changes in hippocampal neurogenesis and related functions need to be addressed experimentally. One interesting feature of ahNG is its susceptibility to pharmacological modulation. Again, based on preclinical data we discuss the possibility that, at least in principle, distinct analgesic drugs commonly used in chronic pain states (typical and atypical opiates, α2δ ligands, and acetyl-L-carnitine) may differentially impact ahNG and that this aspect could be taken into account to reduce and/or prevent the potential risk of cognitive and emotional side effects in the clinical setting.

Keywords: chronic pain, adult neurogenesis, depression, cognition, opiates, tapentadol, pregabalin

Function, dysfunction, and modulation of adult hippocampal neurogenesis

Throughout life, new neurons are generated in the dentate gyrus (DG) of the adult mammalian brain, a process referred to as adult hippocampal neurogenesis (ahNG). In that hippocampal region, the SubGranular Zone (SGZ) acts indeed as neurogenic niche, a permissive and instructive microenvironment where adult neural stem/progenitor cells (aNSC/NPC) survive, self-renew, and give rise to intermediate progenitor cells which, in turn, can generate neuroblasts capable of terminal neuronal differentiation. The surviving adult-born cells will eventually become granule neurons and will be functionally integrated into the DG preexisting circuit.[1–4]

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During the last two decades, extensive research efforts contributed to the concept that adult-born neurons may play a crucial role in several hippocampal-related functions, including selected cognitive functions, pattern discrimination, mood regulation, and stress response.[5–10] It is also of great interest that ahNG appears deregulated in several neurodegenerative and neuropsychiatric disorders, including major depressive disorder (MDD).[11–13]

ahNG is a remarkably modulable process. In animal models, learning, environmental enrichment (EE), and physical exercise have been shown to produce positive effects on proliferation and differentiation of aNSC/NPC as well as survival of their progeny. In parallel, these proneurogenic stimuli ameliorate cognitive performance or anhedonia in animal models of cognitive impairment or stress-induced depressive-like behavior.[14,15] On the contrary, aging and chronic stress exert negative effects on ahNG.[16–18] Intriguingly, reduction of hippocampal neurogenesis has been proposed to potentially contribute to cognitive decline and mood alterations associated with aging and neuropsychiatric disorders.[11–13]

ahNG is also highly susceptible to pharmacological modulation. Antidepressant drugs increase hippocampal neurogenesis in rodents,[19–22] and an increased number of hippocampal NPC and granule neurons are reported in post-mortem brain of MDD patients undergoing antidepressant therapy.[23–25] In addition, several experimental studies demonstrate that antidepressants can counteract the inhibitory effect of stress on ahNG in rodent models of depressive-like disorder.[12,26] Although still debated, it has been proposed that ahNG may be required for some behavioral effects of antidepressants in preclinical models and may potentially contribute to the antidepressant activity of these drugs also in the clinical setting.[27,28] Emerging evidence also suggest that other psychoactive drugs, including the analgesic morphine and several drugs of abuse, result in molecular changes that may negatively affect different aspects of ahNG.[29–31] Also these findings have important clinical implications since they raise the possibility that cognitive dysfunction and/or mood alteration in the setting of such drug use and/or abuse may, at least in part, be correlated with alterations in ahNG.[13]

Deregulated hippocampal neurogenesis in chronic pain states

As listed in Table 1, in rodent models, several preclinical studies have demonstrated a correlation between persistent pain and reduced hippocampal neurogenesis or blunted response of hippocampal NPC to proneurogenic stimuli.[32–37]

Since chronic stress is a well-known negative regulator of ahNG, one may suggest that disrupted ahNG in chronic pain could be merely due to the stress associated with prolonged pain sufferance. On the other hand, it has been convincingly demonstrated that chronic immobilization stress exacerbates the deleterious effects of chronic pain on ahNG, in particular on proliferation and survival of newly generated cells.[36] In a very elegant study, Mutso et al further investigated abnormalities in hippocampal functioning in a persistent pain state.[34] Compared to sham-operated animals, neuropathic mice were proven unable to extinguish contextual fear and displayed increased anxiety-like behavior. Additionally, neuropathic mice displayed decreased hippocampal neurogenesis and altered short-term synaptic plasticity.[34] Intriguingly, the same authors extended their observations to three distinct chronic pain patient subpopulations affected by osteoarthritis (OA), complex regional pain syndrome (CRPS), and chronic back pain (CBP). Compared with controls, CBP and CRPS, but not OA patients, had significantly reduced hippocampal volume bilaterally. Altogether, these findings prompted authors to suggest that hippocampus-mediated behavior, synaptic plasticity, and neurogenesis might be abnormal specifically in neuropathic pain, a clinical condition in which therapeutic approach is particularly challenging. The authors proposed that neuroplastic changes in animal models may be correlated with the reduction in hippocampal volume seen in chronic neuropathic pain patients. Moreover, they suggested that hippocampal abnormalities may potentially underlie learning and emotional deficits commonly observed in patients affected by neuropathic pain.[34]

At present, very limited information is available on the potential mechanisms whereby chronic pain may affect hippocampal neurogenesis and its behavioral consequences. It has been proposed that neuropathic pain induces a cluster of depressive-like symptoms and disrupts hippocampal plasticity via tumor necrosis factor receptor 1 (TNFR1) signaling.[35] When neuropathic pain was induced in mice by sciatic nerve chronic constriction injury (CCI), behavioral effects were associated with impaired hippocampal neurogenesis and reduced expression of several neuroplasticity markers. Temporally, the onset of depressive-like behavior coincided with increased hippocampal TNF levels and decreased expression of TNF R2. Notably, TNFR1^{−/−} mice neither developed depressive-like symptoms after CCI nor developed changes in hippocampal neurogenesis and plasticity, strongly suggesting a role of TNFR1-mediated TNF signaling as a possible regulator of these molecular, cellular, and behavioral events.[35]

Table 1 List of preclinical studies showing reduced or deregulated ahNG in chronic pain states

Species	Chronic pain model	Effects on ahNG	Additional observations	Reference
Rat	Inflammatory pain (CFA)	Reduced BrdU$^+$ cells	Similar to chronic immobilization stress effects	Duric and McCarson[32]
Mice (C57Bl/6)	Neuropathic pain (SNL)	Suppressed proneurogenic effects of EE (reduced DCX$^+$ and NeuroD$^+$ neuroblasts)	No effect on basal ahNG	Terada et al[33]
Mice (C57Bl/6; DCX-EGFP mice)	Neuropathic pain (SNI)	Reduction of DCX$^+$/BrdU$^+$ neuroblasts	Compared to sham animals, in SNI mice: Altered short-term hippocampal synaptic plasticity Inability to extinguish contextual fear and increased anxiety-like behavior	Mutso et al[34]
Mice (C57Bl/6) WT and TNFR1$^{-/-}$ mice	Neuropathic pain (CCI)	Reduced BrdU$^+$/NeuN$^+$ newly generated neurons in WT mice but not in TNFR1$^{-/-}$ mice	TNFR1$^{-/-}$ mice did not develop changes in hippocampal plasticity, and in parallel, depressive-like symptoms No reduced neurogenesis in olfactory bulb	Dellarole et al[35]
Rat	Neuropathic pain (CCI) ± chronic immobilization stress	Reduced proliferation, survival, and neuronal differentiation of newborn hippocampal cells	Immobilization stress exacerbates the negative effect of neuropathic pain on ahNG	Romero-Grimaldi et al[36]
Mice (C57Bl/6)	Inflammatory pain (CFA)	Reduced DCX$^+$/BrdU$^+$ neuroblasts Reduced morphological complexity of newborn cells Effects on ahNG alleviated by EE–VEx	Increasing ventral ahNG alleviates perceptual and affective components of chronic pain Increasing dorsal ahNG alleviates cognitive impairment in chronic pain Overexpression of BDNF in the DG mimicked the effects of EE–VEx	Zheng et al[37]

Abbreviations: ahNG, adult hippocampal neurogenesis; BDNF, brain-derived neurotrophic factor; BrdU, Bromodeoxyuridine; CCI, chronic constriction injury; CFA, complete Freund adjuvant; DCX, doublecortin; DG, dentate gyrus; EE, environmental enrichment; EE–VEx, environmental enrichment + voluntary exercise; NeuN, neuronal nuclear antigen; NeuroD, neurogenic differentiation 1; SNI, spared nerve injury; SNL, spinal nerve ligation; TNFR, tumor necrosis factor receptor; WT, wild-type.

The distinct roles of ahNG in cognition and emotion have raised the interesting possibility that adult-born DG granule neurons may be functionally heterogeneous. The hippocampus is indeed anatomically and functionally dissociated along the dorsoventral (or septotemporal) axis. The dorsal (septal pole) hippocampus is more involved in spatial learning, navigation, and memory, while the ventral (temporal pole) hippocampus may mediate anxiety/depression-related behaviors. Similarly, adult-born neurons in the dorsal hippocampus appear to be required for acquisition of contextual discrimination, whereas those in the ventral hippocampus are required for emotional behavior.[38,39] Cognitive behavioral therapy, such as EE and voluntary exercise (EE–VEx), is under investigation as a nonpharmacological approach for chronic pain. By using a mouse model of inflammatory pain, Zheng et al demonstrated a distinct contribution of ahNG along the dorsoventral axis to EE–VEx's beneficial effects on different dimensions of chronic pain.[37] Adult neurogenesis in the ventral hippocampus appeared to contribute to EE–VEx-mediated beneficial effects on perceptual and affective components of chronic pain. Conversely,

neurogenesis in the dorsal hippocampal pole was involved in EE–VEx cognitive-enhancing effects in chronic pain.[37]

As it always occurs in emerging and controversial research fields, recently Apkarian et al published an interesting paper which raised additional questions about the meaning of ahNG alterations in chronic pain states.[40] The authors manipulated hippocampal neurogenesis by several different approaches (pharmacologically, by X-irradiation, and by the use of genetically modified mice displaying increased or decreased ahNG) and tested its influence on both inflammatory and neuropathic pain-like behaviors. Surprisingly, they reported that downregulation of ahNG reversibly diminished persistent pain, while upregulation resulted in prolonged persistent pain.[40] Based on these findings, they actually proposed that ahNG-mediated learning mechanisms may be involved in the development of persistent pain.[40] This is the first proposal of a potentially active role of neurogenesis in pain modulation. In light of these results, future studies should more carefully dissect the contribution of ahNG to development, maintenance, and resolution of chronic pain states.

Potential clinical implications for deregulated ahNG in chronic pain states

Chronic pain is a highly debilitating disease state. Clinical observations demonstrate that many patients affected by chronic pain exhibit increased anxiety and depression, suggesting the importance of affective or emotional pain components.[41–43] Consistent with the concept of pain matrix, functional imaging studies also suggest that shared neural mechanisms may contribute to the comorbidity between chronic pain and anxiety/depression. In addition, there is clinical evidence that chronic pain may impair various aspects of cognition, including cognitive flexibility and memory capacities.[44,45] Our current understanding of the molecular and cellular events that may underlie the comorbidity of chronic pain, depression, and cognitive impairment is still very limited. If and how persistent pain may affect potential brain areas, like the hippocampus, implicated in both cognition and emotional aspects has been largely unexplored. The occurrence of extensive preclinical evidence suggesting that chronic pain may induce profound changes in hippocampal plasticity, including deregulated hippocampal neurogenesis, should be further studied and addressed mechanistically. Based on a vast array of research observations, it is possible that dysregulated ahNG in chronic pain states may contribute, at least in part, to cognitive deficits and mood alterations in patients.

An additional aspect that should be taken into consideration for its clinical implications is the different impact of distinct therapeutic interventions in chronic pain. Preclinical data mark the importance of taking into account inhibition of ahNG as a potential long-term consequence of some opiates. Indeed since the initial report,[29] extensive experimental data have been accumulated on the negative impact of chronic morphine administration on ahNG mainly via μ-opioid receptors (MORs).[31,46–51] The deleterious effect of morphine on hippocampal neurogenesis may potentially represent, among others, one mechanism by which morphine and other opiates exert long-lasting effects on the neural circuitries involved with cognition and mood regulation. Incidentally, cognitive dysfunction has been often reported in opiate drug abusers.[48,52] Moreover, recent work has suggested an association between prolonged opiate use and the risk of new onset depression.[53,54] Interestingly though, some atypical opiates do not negatively influence adult NSC and their progeny, at least in preclinical models. An in vivo study in the rat reported that chronically administered methadone does not reduce ahNG.[55] Methadone is a strong opioid analgesic which, at clinically achievable concentrations, can also inhibit functional N-methyl-D-aspartate (NMDA) receptors,[56] and NMDA antagonists can produce positive effects on hippocampal neurogenesis in rodents.[57,58] Whether this pharmacological property of methadone may explain its lack of negative effects on ahNG likely deserves further investigation. In a similar manner, tapentadol, the first representative of a novel analgesic drug class referred to as MOR-NRI (MOR agonist and noradrenaline reuptake inhibitor), did not reduce hippocampal neurogenesis when chronically administered in adult mice at a clinically relevant dose.[59] It has been suggested that the noradrenergic component in tapentadol has the potential to counteract the adverse MOR-mediated effects on ahNG both in vivo and in vitro.[59]

Altogether, based on preclinical data, different risks of negative impact on ahNG are associated with distinct opiates which are commonly used in patients affected by chronic pain.[31] At least in principle, the long-term use of analgesic drugs that do not cause dysfunction of ahNG may, in turn, result in less disruption of neurogenesis-associated functions in chronic pain patients. It should also be underlined that analgesic drugs which rather increase ahNG in preclinical models could be taken into consideration, at least in neuropathic pain where they are very effective. Indeed, the α2δ ligands pregabalin/gabapentin[61] and acetyl-L-carnitine[62] have been demonstrated to significantly promote hippocampal neurogenesis in rodents. Interestingly, both drugs act via modulation of NF-κB-mediated signaling, a pathway that has been shown to play a crucial role in the regulation of ahNG in response to several signals and drugs.[61–67] Interestingly, both α2δ ligands and acetyl-L-carnitine also exert antidepressant activity in rodent where depressive-like behavior was induced by chronic restraint or unpredictable chronic mild stress.[61,62,68] Interestingly, the same drugs also produce antidepressant effects in patients.[69,70] Again, at least in principle, analgesic drugs that promote ahNG could represent first option therapy since they may have beneficial effects also on emotional and, potentially, on cognitive aspects in chronic pain states. At present, no clinical data are available to support this hypothesis since this approach would require to monitor neurogenesis in vivo, and no such imaging techniques are currently applicable in human studies. On the other hand, in vivo imaging of neurogenesis has been achieved in mice using transgenic model systems supporting the idea that in a near future detection of neurogenesis could theoretically be achieved in humans using current imaging devices.[71]

Altogether, based on several preclinical observations, in the future, more studies should be devoted to a better

understanding of how analgesic drugs differentially affect molecular and cellular aspects of ahNG and hippocampal function. Currently, several compounds acting at different targets are under development for effective chronic pain treatment.[72–74] Potentially, future drug design may take into consideration the development of powerful analgesics that, by preserving or even promoting ahNG, may reduce the risk or prevent cognition and mood alterations in chronic pain patients.

Disclosure

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