Review

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A ventral view on antidepressant action: roles for adult hippocampal neurogenesis along the dorsoventral axis

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Adult hippocampal neurogenesis is implicated in antidepressant action, stress responses, and cognitive functioning. The hippocampus is functionally segregated along its longitudinal axis into dorsal (dHi) and ventral (vHi) regions in rodents, and analogous posterior and anterior regions in primates, whereby the vHi preferentially regulates stress and anxiety, while the dHi preferentially regulates spatial learning and memory. Given the role of neurogenesis in functions preferentially regulated by the dHi or vHi, it is plausible that neurogenesis is preferentially regulated in either the dHi or vHi depending upon the stimulus. We appraise here the literature on the effects of stress and antidepressants on neurogenesis along the hippocampal longitudinal axis and explore whether preferential regulation of neurogenesis in the vHi/anterior hippocampus contributes to stress resilience and antidepressant action.

The hippocampus and adult hippocampal neurogenesis

The hippocampus is heterogeneous in function, playing central roles in learning and memory, emotional processes, and the regulation of glucocorticoid release (see Glossary) by the hypothalamic–pituitary–adrenal (HPA) axis [1]. In the mammalian brain, the hippocampus is one of only a few brain areas where neurogenesis (Box 1), the birth of new neurons, takes place throughout postnatal life [2]. Adult hippocampal neurogenesis has been shown to contribute to the behavioural effects of antidepressant drugs, restoration of glucocorticoid concentrations following stress and antidepressant treatment, as well as to some hippocampus-dependent cognitive processes including spatial learning and memory [3–5]. Recent attention has focused on distinct separation of hippocampal function along its longitudinal axis (Figure 1). In rodents, the vHi (analogous to human anterior hippocampus) plays a preferential role in the stress response and anxiety, whereas the dHi (analogous to human posterior hippocampus) is preferentially involved in spatial learning and memory. Given that adult hippocampal neurogenesis is important in processes preferentially regulated by the dHi or the vHi, it is possible that neurogenesis is also preferentially regulated in these specific subregions depending upon the stimulus. Moreover, because adult hippocampal neurogenesis is implicated in the mechanism of antidepressant action [6–8], and that the vHi is connected to structures that regulate key processes that are dysfunctional in depression (Figure 2), it is plausible that neurogenesis in the vHi rather than in the dHi might be a crucial component in the treatment of depression. Furthermore, differential regulation of neurogenesis along the longitudinal axis of the hippocampus could potentially allow adult hippocampal neurogenesis to be selectively harnessed as a therapeutic strategy for either stress-related psychiatric disorders such as depression, or for particular cognitive dysfunctions. Thus, the purpose of the present review is to critically appraise the current literature on the effects of stress, depression, and antidepressant action on adult neurogenesis along the longitudinal axis of the rodent and human hippocampus, and to offer insight into how this relationship should be explored further using animal models and clinical neuroimaging.

Segregation of the hippocampus along its longitudinal axis: anatomical and genomic clues

Studies demonstrating that the rodent hippocampus has distinct anatomical connections along its dorsoventral axis provided the first hint that the hippocampus might be functionally segregated along its longitudinal axis ([1,9,10] for review). In rodents, the dHi and vHi exhibit distinct afferent and efferent connectivity (Figure 2). The dorsal CA1 sends projections to structures primarily involved in the processing of visuospatial information, spatial memory, and spatial exploration and navigation, whereas the vHi is anatomically connected to structures that regulate neuroendocrine and behavioural responses to stress, anxiety, reward processing, motivation, and executive function, processes that are frequently disrupted in depression (Figure 2). Functional neuroimaging studies suggest that a similar dichotomy in anatomical connectivity occurs

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Glossary

Agomelatine: a recently developed antidepressant drug that acts as a melatonin receptor agonist and a 5-HT_{2C} receptor antagonist.
Amygdala: a brain structure that plays a key role in fear learning and anxiety.
Anterior cingulate cortex (ACC): an area of cortex that receives projections from the dorsal CA1 and the dorsal subiculum of the hippocampal formation, and plays a role in visuospatial memory. Through connections with other brain areas, the ACC also plays an important role in determining the salience of emotion and motivational information, and in the emotional reaction to pain.
Bed nucleus of the stria terminalis (BST): an area of the brain that serves as a relay and integration centre between nuclei involved in the regulation of reward, stress, and anxiety. It is a major output pathway of the amygdala to the hypothalamus, and it also serves as a relay centre for hippocampal regulation of the HPA axis in response to stress.
BrdU/NeuN-positive cells: dual immunolabelling of BrdU (bromodeoxyuridine) and NeuN (neuronal nuclear antigen) is used to identify recently generated cells that have developed into mature neurons. BrdU is an exogenous chemical that is administered to label dividing cells. It acts as a thymidine analogue that becomes incorporated into the DNA of dividing cells. Depending upon the timing of its administration, BrdU can be used to measure rates of proliferation or survival of newlyborn cells. The phenotype of BrdU-labelled cells can be determined by coupling BrdU immunohistochemistry with immunohistochemistry of other cell markers such as NeuN. NeuN is a marker of mature neurons, and its expression becomes apparent as the expression of doublecortin begins to decline. Thus, BrdU/NeuN immunohistochemistry can be used to identify newly generated cells that have developed into mature neurons.
Corticosterone: the glucocorticoid in rodents that regulates the stress response. In humans, cortisol is the glucocorticoid that plays this same role.
Cytogenesis: the proliferation of new cells.
Doublecortin-positive cells: doublecortin protein is used as a marker of immature neurons. Maturing neuronal cells express doublecortin for 2 or 3 weeks following their birth. Neuronal precursor cells also express doublecortin while dividing.
Hypothalamus: a brain structure comprised of a group of smaller nuclei which secrete hormones and thus link the central nervous system with the endocrine system. It regulates the neuroendocrine response to stress via the HPA axis, and is also involved in the regulation of other processes such as feeding and sexual behaviour as well as body temperature.
Hypothalamic–pituitary–adrenal axis (HPA axis): the neuroendocrine system that regulates the response to stress. It involves the release of corticotropin-releasing hormone (CRH) and vasopressin from the paraventricular nucleus of the hypothalamus, which in turn stimulate the secretion from the pituitary gland of adrenocorticotropic hormone (ACTH), which then acts on the adrenal cortex to produce the glucocorticoid hormones, cortisol in humans and corticosterone in rodents. Glucocorticoids exert negative feedback on the hypothalamus and pituitary (as well as the hippocampus) thus reducing further glucocorticoid release. A subset of depressed patients exhibit overactivity of the HPA axis and impairment of its negative feedback control mechanism.
***In vivo* amperometry:** a technique in which an electrode is inserted into the brain of a freely behaving animal for the purposes of measuring changes in extracellular fluid concentrations of neurotransmitters and other substances such as glucose and oxygen in real time.
Optogenetics: a technique which uses a combination of light and gene technology to turn specific neurons on and off with millisecond precision in the brain of freely behaving animals.
Long-term depression (LTD): a form of synaptic plasticity that decreases the strength between synapses.
Long-term potentiation (LTP): a form of synaptic plasticity involving long-term strengthening of synapses between neurons when they have been activated simultaneously.
Magnetoencephalography (MEG): a clinical neuroimaging technique that allows mapping of neural activity by measuring small magnetic fields associated with electrical activity in the brain.
Mammillary nuclei: brain structures mainly concerned with spatial direction.
Medial prefrontal cortex (mPFC): a brain region which plays an important role in processing convergent cognitive and emotionally relevant information, and makes decisions as to how to appropriately respond to this information. Within this role, it regulates the HPA axis response to psychological stress and is involved in fear information processing. The infralimbic cortex area of the mPFC plays an important role in extinguishing a learned fear memory (fear extinction). Disrupted fear extinction is associated with the anxiety disorder, post-traumatic stress disorder. By contrast, the prelimbic cortex area of the mPFC plays a role in fear expression.
Nucleus accumbens: a brain area that plays a key role in reward processing and in the motivation of feeding behaviour. It plays an important role in drug addiction, and recent small clinical studies suggest that electrode stimulation of this brain area has antidepressant effects.
Place field: when an animal enters a specific place in its environment, one or more neurons in the hippocampus become activated. Specific neurons respond to specific locations. Neurons that are activated in response to a specific location are termed place cells. The area in which the neuron is activated the most is the place field of that neuron.
Prenatal restraint stress: a model of early-life stress whereby pregnant mice or rats are restrained in a transparent cylinder several times per day for much of their pregnancy. The offspring of these dams exhibit depression-related neurobiological and behavioural alterations that persist into adulthood, including impaired feedback mechanisms of the HPA axis, increased stress sensitivity, disruption of circadian rhythms, and altered neuroplasticity.
Retrosplenial cortex (RSP): an area of cortex that receives projections from the dorsal CA1 and the dorsal subiculum; the RSP processes visuospatial information and is involved in visuospatial memory.
Social defeat stress: a model of psychosocial stress wherein an intruder mouse is periodically subordinated or defeated by an aggressive resident mouse. The test mouse is also forced to spend the remainder of a 24 h period in the same cage as the aggressor but is separated from the aggressor by a partition that allows olfactory, visual, and auditory contact but offers physical protection. Chronic social defeat stress results in social withdrawal behaviour in non-threatening situations as well as several other behavioural and physiological changes characteristic of depression.
Subiculum: the most inferior component of the hippocampal formation and the main output station of the hippocampus.
Unpredictable chronic mild stress (UCMS): an animal model of chronic stress involving long-term exposure to a series of mild but unpredictable stressors which results in several behavioural and physiological changes that are also observed in depression, such as anhedonia.
Ventral tegmental area (VTA): a brain structure that contains the dopamine neurons which form the mesocorticolimbic dopamine system which plays an important role in the reward circuitry of the brain. Disruption of the mesocorticolimbic dopamine system is thought to contribute to the inability to experience pleasure (termed anhedonia), a characteristic of depression. The VTA has also been shown to play an important role in locomotion and may contribute to visuospatial processes.

in the anterior and posterior regions of the hippocampus in humans, areas that are analogous to the rodent vHi and dHi, respectively [9].

In addition to this segregation in anatomical connectivity, recent transcriptomic studies have demonstrated genomic heterogeneity along the dorsoventral axis of the CA1, CA3, and dentate gyrus areas of the mouse hippocampus [1,11–14], and the granule cell layer of the rat hippocampus [15]. For example, in the mouse dentate gyrus, the gene encoding lactase, *Lct*, is preferentially expressed in the dorsal region, whereas the thyrotropin releasing hormone receptor gene, *Trhr*, is expressed specifically in the ventral region, and the expression of both genes is relatively limited in the intermediate portion of the hippocampus. Thus, it has been suggested that the rodent hippocampus is composed of three distinct molecular domains – dorsal, intermediate, and ventral [1]. Whether such genomic heterogeneity is directly related to the dichotomy in function of the dHi and vHi, and whether similar genomic variations occur along the longitudinal axis of the hippocampus of primates and humans, has yet to be determined, although a recent study suggests that there are differences in gene expression between the hippocampus of mice and humans [10,16].

Segregation of the hippocampus along its longitudinal axis: functional evidence

The hypothesis that the hippocampus is functionally segregated along its longitudinal axis was first proposed by Moser and Moser, who also provided direct evidence for this phenomenon in rodents [17]. This functional segregation of the hippocampus along its longitudinal axis has since been supported by lesion, optogenetic, and electrophysiological studies in rodents (Figure 2), and more