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Review

The common properties of neurogenesis in the adult brain: from invertebrates to vertebrates☆

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Abstract

Until recently, it was believed that adult brains were unable to generate any new neurons. However, it is now commonly known that stem cells remain in the adult central nervous system and that adult vertebrates as well as adult invertebrates are currently adding new neurons in some specialized structures of their central nervous system. In vertebrates, the subventricular zone and the dentate gyrus of the hippocampus are the sites of neuronal precursor proliferation. In some insects, persistent neurogenesis occurs in the mushroom bodies, which are brain structures involved in learning and memory and considered as functional analogues of the hippocampus. In both vertebrates and invertebrates, secondary neurogenesis (including neuroblast proliferation and neuron differentiation) appears to be regulated by hormones, transmitters, growth factors and environmental cues. The functional implications of adult neurogenesis have not yet been clearly demonstrated and comparative study of the various model systems could contribute to better understand this phenomenon. Here, we review and discuss the common characteristics of adult neurogenesis in the various animal models studied so far. © 2002 Published by Elsevier Science Inc.

Keywords: Adult neurogenesis; High vocal center; Hippocampus; Learning and memory; Mushroom bodies; Subventricular zone; Growth factors; Hormones; Neurotransmitters; Environmental cues

1. Introduction

The formation of the nervous system has been widely studied during development in species and models from different evolutionary origins as invertebrates, amphibians, birds and mammals. However, although the study of brain maturation in adult animals has long been ignored, it is now clear that central nervous system plasticity does not stop at the end of development. The ability of an animal to adapt its behavior to an infinity of environmental situations reflects a degree of functional, but also probably structural brain plasticity. Furthermore, the quality of environment, i.e. the variety of sensory stimuli has been shown to influence the ratio synapses/neurons and to modulate neuronal survival (Turner and Greenough, 1985). Axogenesis and synaptogenesis have been observed in adults and, even in the absence of any pathological process, synaptic remodelling occurs in response to physiological cues (hormonal titers, stress, neuronal activity...) (Theodosis and Poulain, 1993; Frankfurt, 1994). Thus, the dogma of the

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neural fixity in the brain of adult animals is no more a question of the day, especially since production of new neurons, or secondary neurogenesis, has been demonstrated in the brain of various adult invertebrate and vertebrate species (including humans).

Indeed, although Altman evoked the possibility of a persistent neurogenesis in the brain of adult rodents as early as 1962, this observation remained unnoticed until 1977 when Kaplan and Hinds, using electron microscopy, confirmed the neuronal fate of the newly generated cells in the dentate gyrus and in the olfactory bulb (Kaplan and Hinds, 1977). Concomitantly, several studies on non-mammalian vertebrates (amphibians, fish, reptiles, birds) showed that new neurons were produced during the whole life, especially in structures involved in vision (John and Easter, 1977; Raymond and Easter, 1983; Chetverukhin and Polenov, 1993). Finally, our group showed for the first time that, even in insects, the nervous system of which had often been considered as particularly inflexible, neurogenesis still persists in adults (Cayre et al., 1994, 1996a).

Recently, the discovery of cell proliferation and neuronal production in human hippocampus (Eriksson et al., 1998) aroused interest of the neurobiologists.

2. Where does secondary neurogenesis occur?

2.1. In invertebrates

In some insect species, new interneurons continue to be added throughout adulthood in the main associative centre of the insect brain, the mushroom bodies. These structures are involved in the integration of multisensorial inputs from the antennae, the complex eyes and the palpae (Kenyon, 1896; Erber, 1978; Mobbs, 1982; Li and Strausfeld, 1997). It is a paired structure consisting in densely packed intrinsic neurons: the Kenyon cells, and differentiated neuropils.

The neuropil is typically divided into the calyx (a single or double formation that is often cup-shaped), the peduncle and its two main arbors: a vertical one comprising the α and α' lobes and a medial one composed of β, β' and γ lobes (Fig. 1). The shapes and the relative sizes of the mushroom body neuropilar parts characterize the taxonomic groups.

This neuropil includes the projections of Kenyon cells and their synaptic contacts with afferent and efferent neurons. In the last two decades, mushroom bodies were demonstrated to show striking morphological plasticity in adult insects. Changes in neuropil volumes were reported according to the insect age or experience in species as different as *Aleochara* (Coleoptera), *Drosophila* (Diptera) or *Apis* (Hymenoptera) (Bieber and Fuldner, 1979; Technau, 1984; Durst et al., 1994; Heisenberg et al., 1995; Withers et al., 1993). Dujardin (1850) who first described mushroom bodies, postulated a role for these structures as the centre of 'insect intelligence'. Numerous experimental approaches in various insect species such as genetic or chemical ablation of mushroom bodies in *Drosophila* (Heisenberg et al., 1995; de Belle and Heisenberg, 1994; Liu et al., 1999), local cooling of mushroom bodies in the honeybee (Erber et al., 1980) or microlesions in the cockroach (Mizunami et al., 1993, 1998) demonstrated their role in olfactory, spatial and contextual learning.

Persistent neurogenesis in mushroom bodies of adult insects has been described in several species of *Orthoptera* and *Coleoptera*, in the milkweed bug (Cayre et al., 1994, 1996a) and in the praying mantis (unpublished). Contradictory results were published concerning the occurrence of neurogenesis in the adult American cockroach (Cayre et al., 1996a; Gu et al., 1999). However, neurogenesis was not found in the brain of the adult honeybee (Fahrbach et al., 1995), the fruitfly (Ito and Hotta, 1992), the monarch butterfly (Nordlander and Edwards, 1970) and the migratory locust (Cayre et al., 1996a). In these species, the neuroblasts at the origin of mushroom body formation stop dividing and degenerate during the last preimaginal instar (Farris et al., 1999; Ganeshina et al., 2000). By contrast, in crickets, a cluster of approximately 100 neuroblasts located at the apex of the cortex of the mushroom bodies produce new Kenyon cells during the whole insect life. Waves of newly formed cells migrate into the depth of the cortex and take their place among the older interneurons from which they cannot be distinguished, their cell bodies having comparable shape and size within the usual columnar arrangement (Cayre et al., 2000). This seems to be a quantitatively important phenomenon, since BrdU labeling allowed to estimate that approximately 25% of the total number of Kenyon cells in the mushroom body of 40-day-

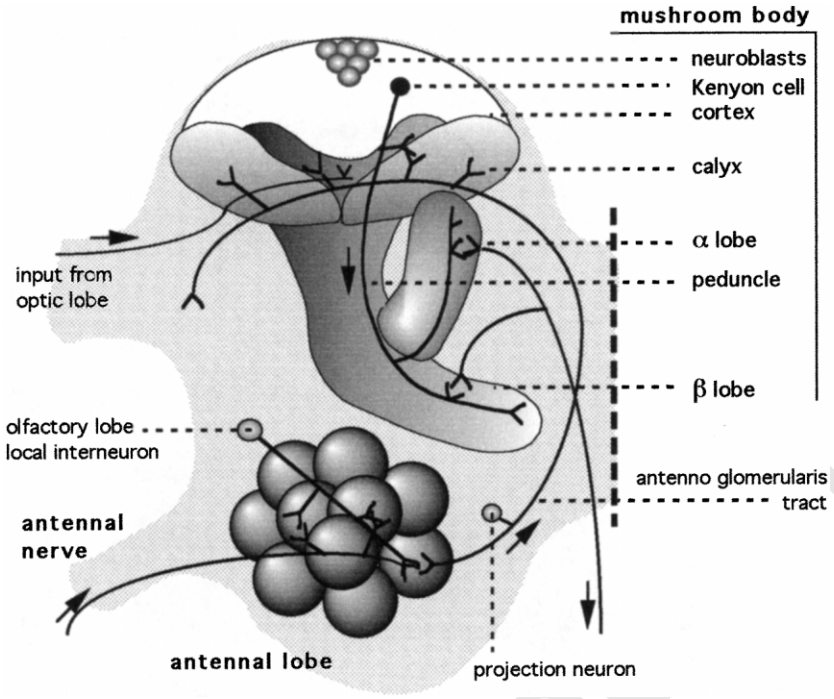

Fig. 1. Schematic representation of a mushroom body in a cricket hemi-brain (frontal view). Kenyon cells, the mushroom body intrinsic interneurons, fill the cortex and send their neurites into the calyx and through the peduncle to the α and β lobes (subdivisions α′, β′ and γ have been omitted). A cluster of neuroblasts located at the apex of the mushroom body cortex keeps producing new interneurons throughout the insect life. The mushroom body receives visual/olfactory information from the optic/antennal olfactory lobes.

old crickets were produced during adulthood (Cayre et al., 1996a).

There is no clear explanation why neurogenesis persists in some insect species and is absent from others. Phylogenesis does not seem to be a good criterion since adult locusts that are phylogenetically close to crickets do not keep proliferating neuroblasts whereas some holometabolous species such as *Tenebrio* or *Harmonia* present a neurogenesis pattern similar to crickets. Behavioral complexity has also been suggested as a criterion for the necessity of persistent neurogenesis (Bieber and Fuldner, 1979). However, this hypothesis is not satisfying because social insects such as ants or bees, exhibiting the most sophisticated behavioral repertoires are lacking secondary neurogenesis. In these species however, mushroom bodies still show remarkable plasticity through sprouting and synaptogenesis (Withers et al., 1993). Thus, whatever the strategy used (secondary neurogenesis or increased synaptic contacts), mushroom bodies display continuous remodelling during the whole insect life. Such morphological and structural changes probably underly functional plasticity.

In decapod crustaceans, neurogenesis occurs among the different neuronal types of the central olfactory pathway throughout adult life suggesting structural plasticity of the brain circuitry (Schmidt and Harzsch, 1999). For example, in crayfish brain, new interneurons are added to two bilateral clusters of neurons associated with olfactory and accessory lobes (Sandeman and Sandeman, 2000). In adult shore crab, new cells are produced in the hemi-ellipsoid bodies which are the target neuropils of the olfactory projection neurons (Schmidt, 1997). This structure has been suggested to be homologous to the insect mushroom bodies and seems to be the most important multimodal association centre in crustaceans (Strausfeld et al., 1998).

2.2. In non-mammalian vertebrates

Among fish, some species, such as gymnotiform fish, keep growing as adults. In the brain of these

fish, continuous growth can extensively be attributed to addition of new cells, both neurons and glia. Zones of high proliferative activity are typically located at or near the surface of the ventricular, paraventricular and cisternal systems. For example, the central posterior/prepacemaker nucleus, a bilateral cluster of neurons involved in the control of the electric organ, shows a high proliferative activity in an area near the wall of the third ventricule (Zupanc and Zupanc, 1992). New cells are produced at an equally high rate in the molecular layer of the cerebellum and migrate to their specific granular layer target (Zupanc and Horschke, 1995). Studies have shown that proliferation activity is related to age, decreasing in old animals (Kranz and Richter, 1975). Interestingly, apoptosis occurs concomitantly to neurogenesis and thus could regulate the rate of birth of newly formed cells (Soutschek and Zupanc, 1996; Zupanc, 1999a). In the goldfish visual system, apart from the retina, neurogenesis occurs in the optic tectum during adulthood. Most new cells are generated in a germinative area located in the caudal part of the tectum, then migrate to reach the rostral part of the tectum (Raymond and Easter, 1983). Moreover, it has been suggested that the activity of the retinal afferent fibres in the optic nerve could regulate the rate of mitotic activity of the progenitor cells (Raymond et al., 1983).

In the adult frog, new cells are continuously generated in the preoptic recess ventricular zone then are recruited in an area of the hypothalamic preoptic nucleus (Chetverukhin and Polenov, 1993).

Postnatal neurogenesis also occurs in both lizard and turtle telencephalon (Perez-Canellas and Garcia-Verdugo, 1996; Perez-Canellas et al., 1997) and the most intense neuronal production is observed in the medial cortex of the lizard which has homology with the hippocampal fascia dentata of mammals. The ependymal cell layer underlying the medial cortex keeps its proliferative germinal properties in adulthood and continues to produce new cells (Lopez-Garcia et al., 1988). Immature migratory neurons are then recruited in the granular layer and send axons to their targets (Lopez-Garcia et al., 1990). Other telencephalic regions of the lizard brain such as the olfactory bulb or the nucleus sphericus keep a high rate of postnatal neurogenesis (Perez-Sanchez et al., 1989; Garcia-Verdugo et al., 1989).

In birds, neuronal progenitors are located in discrete proliferative regions ('hot spots') in the walls of the lateral ventricles and these produce new neurons during the entire life of the animal. These neurons migrate in several areas of the telencephalon, especially in the high vocal center (HVC), a nucleus involved in song production (Goldman and Nottebohm, 1983). The newborn HVC neurons project specifically into the robustus archistriatalis (RA). Radial fibers guide the newly formed neurons towards their final destination, and migration is helped by a down regulation of the expression of cell adhesion molecules such as NCAM (Alvarez-Buylla, 1990; Barami et al., 1994). Thus, the migration speed is fairly high, approximately 28 μm/h (Alvarez-Buylla, 1990). After migration, these cells differentiate (Alvarez-Buylla and Nottebohm, 1988) and are recruited into functional circuits (Patton and Nottebohm, 1984). The recruitment of new HVC neurons is part of a replacement process, and it has been shown that peaks of cell death precede peaks of neurogenesis (Kirn and Nottebohm, 1993; Kirn et al., 1994). Recently, clear evidence has been given that targeted death of RA-projecting neurons induces recruitment of new neurons in HVC (Scharff et al., 2000).

2.3. In mammals

In mammals, secondary neurogenesis occurs in two distinct brain areas, the subventricular zone (SVZ) lining the lateral ventricle (Fig. 2a), and the subgranular zone of the dentate gyrus (Fig. 2b) (Altman, 1962; Kaplan and Hinds, 1977; Kaplan and Bell, 1984). Unlike birds, where the cells generated in the ventricular zone migrate to most of telencephalic areas, in mammals, the neurons born in the SVZ migrate almost exclusively in the olfactory bulb, via the rostral migratory stream, where they differentiate into interneurons (Corotto et al., 1993). However, a recent study demonstrated that, in macaques, a few cells migrate through the white matter into cortical areas (Gould et al., 1999a). Biebl et al. (2000) showed a high number of apoptotic cells in the rostral migratory stream especially towards the olfactory bulb and concluded that the majority of the cells generated in the SVZ are eliminated after reaching their target area. A recent study revealed that a well-developed SVZ exists in the adult human brain, but no clear evidence of a persistent

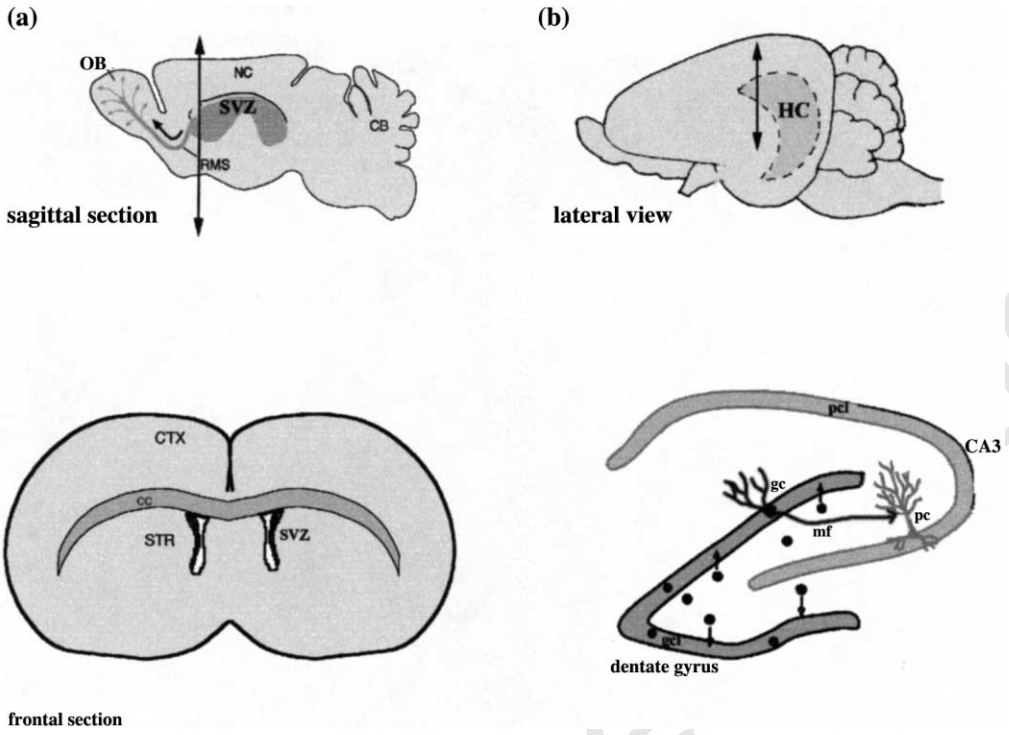

Fig. 2. Areas of neurogenesis in the adult mammalian brain. (a) Schematic view of the subventricular zone (SVZ) where neural progenitor cells proliferate. Newly formed cells then migrate along the rostral migratory stream (RMS) toward the olfactory bulb (OB). In the frontal section, the SVZ appears lining the wall of the lateral ventricle. (b) Location of the hippocampus (HC) in the rodent brain (lateral view). Drawing of a frontal section of the hippocampus showing the dentate gyrus granule cell layer (gcl) where neurogenesis occurs. Newly formed granule cells (gc) contact pyramidal cells (pc) in the CA3 region of the hippocampus. NC: neocortex; CB: cerebellum; mf: mossy fibers; pcl: pyramidal cell layer; CTX: cortex; STR: striatum; cc: corpus callosum.

neurogenesis has yet been provided (Bernier et al., 2000).

In the hippocampus, the proliferative cells are located in a germinal zone along the border between the granule layer and the hilus of the dentate gyrus (Altman and Bayer, 1990), and give rise to new granular cells and glial cells. In this case, the migration is thus reduced. However, newborn neurons transiently express the polysialylated neural cell adhesion molecule (PSA-NCAM) which helps cell movement by inhibiting cell-to-cell adhesion (Seki and Arai, 1992). Quantitatively, it has been estimated that this secondary neurogenesis produces several thousands granule neurons per day, or the equivalent of one new neuron for 2000 pre-existing granule cells per day. In rats, the number of granule cells in the dentate gyrus thus increases until the animal is 6 months old, and then stabilizes due to concomitant cell death.

It should be underlined that in all vertebrate models (fish, birds and mammals), neurogenesis and apoptosis occur simultaneously and appear to be tightly linked together, cell death being a possible factor triggering neural precursor proliferation (Zupanc, 1999a; Scharff et al., 2000; Gould and Tanapat, 1997).

3. Stem cells and progenitor cells

The occurrence of secondary neurogenesis implies that neural stem cells are not only present in the developing nervous system but also in the adult nervous system. The term ‘neural stem cell’ is used for a cell that presents two main properties: it should be able to divide symmetrically to generate high numbers of identical cells (multiplication, expansion), and to divide asymmetrically to produce progenitor cells which in turn will give rise to different cell types such as neurons and

glial cells (multipotentiality) (for review, see Gage, 2000; Momma et al., 2000).

In adult insects, mushroom body dividing cells mainly give rise to interneurons, although the production of some glial cells has not been ruled out. However, they are usually called 'neuroblasts' conferring upon them a status of progenitor cells rather than stem cells. During development, mushroom body neuroblasts divide both symmetrically in order to expand the population of dividing cells and asymmetrically to produce smaller 'ganglion mother cells' which will themselves divide only once to give rise to Kenyon cells (Nordlander and Edwards, 1970; Ito and Hotta, 1992). In adults, it seems that neuroblasts mainly divide asymmetrically.

Use of multiple immunocytological labeling for cell proliferation (BrdU) and for cell type markers (NSE, calbindin, nestin, NeuN, GFAP, etc...), and more recently the development of retroviral infection techniques, showed that dividing cells in the adult brain produce both neurons and glia, in birds as in mammals (Goldman et al., 1996; Reynolds et al., 1992; Reynolds and Weiss, 1992; Lois and Alvarez-Buylla, 1993). It is not yet quite clear how many steps there are between the stem cell and the cell committed in a differentiation process. Recently, progenitor cells have been isolated from the dentate gyrus of adult human brain (Roy et al., 2000). Thus, the adult human hippocampus contains mitotically competent neural progenitors that can be selectively extracted.

Several studies tried to determine which cells were the stem cells in the SVZ, and the results were rather controversive. The germinative area of the SVZ is mainly constituted of four distinct cell types: ependymal cells facing the lumen of the ventricle, migrating neuroblasts (type A cells) surrounded by astrocytes (type B cells), and, lastly, clusters of dividing cells (type C cells) tightly linked to neuroblasts. Johansson et al. (1999) provided evidence that the stem cells were the ependymal cells, whereas the paper of Doetsch et al. (1999) presented convincing experiments suggesting that the type B glial cells would be the real stem cells of the SVZ. The authors presume that such discrepancies could proceed from the different experimental procedures used.

In vitro studies of stem cells largely contributed to our knowledge of these cells. The role of growth factors on progenitor mitotic activity has received much attention. It has thus been shown that addition of FGF-2 or EGF in the culture medium considerably induced the proliferation of progenitor cells, allowing the production of clonal cell lines from hippocampus or SVZ of adult rodents (Reynolds and Weiss, 1992; Gage et al., 1995; Ray et al., 1997), whereas BDNF rather acted as a survival factor for newly generated neurons (Kirschenbaum and Goldman, 1995). More strikingly, using these growth factors, it was possible to induce cell proliferation even in non-neurogenic areas of the adult central nervous system such as cortex, striatum or septum (Richards et al., 1992; Reynolds and Weiss, 1992). Thus, a new concept of the brain organization emerged: progenitor cells are present in almost all regions of central nervous system, as proven by the ability to culture them, but in vivo their proliferative potentialities are only observed in two particular areas (SVZ and dentate gyrus), probably due to the presence of mitogenic factors in their close environment. Otherwise, these cells remain in a quiescent state.

4. In vivo regulation of secondary neurogenesis

Neuroblast proliferation and survival of newly formed neurons appear to be regulated by both internal (hormones, neurotransmitters, growth factors...) and environmental (seasons, sensorial stimuli...) cues.

4.1. Internal factors

4.1.1. In invertebrates

In adult insects, mushroom body neurogenesis is clearly regulated by hormones. The steroid hormone ecdysone, synthesized by oocytes, inhibits Kenyon cell production (Cayre et al., 1997a). By contrast, juvenile hormone (JH), a sesquiterpene involved in larval moulting during development and in ovary maturation in adult, stimulates neuroblast proliferation (Cayre et al., 1994). Mitogenic action of JH has been shown to be mediated by putrescine, a short-chain polyamine: the stimulatory action of JH on neuroblast proliferation was prevented by a specific inhibitor of polyamine biosynthesis, but putrescine feeding of JH-deprived animals was able to mimic the effect of JH (Cayre et al., 1997b).

4.1.2. In non-mammalian vertebrates

In non-mammalian vertebrates, the neuropeptide somatostatin seems to be an important regulator

key for neurogenesis in adult brain. The distribution pattern of somatostatin and its binding sites match with sites of proliferative activity, migration and differentiation in the cerebellum and in the central posterior/pre-pacemaker nucleus in adult gymnotiform fish (Zupanc, 1999a). In mammal brain, somatostatin and somatostatin receptors are transiently expressed in the immature rat cerebellar cortex and postnatally disappear (Gonzalez et al., 1992). Therefore, it could be argued that expression of somatostatin and its receptor is related to postnatal neurogenesis in gymnotiform fish. Moreover, regenerative studies have shown a somatostatin-immunoreactivity increase after lesion in both gymnotiform fish and lizard (Molowny et al., 1995; Zupanc, 1999b).

4.1.3. In mammals

In the mammalian brain, several neuroendocrine factors that regulate neurogenesis in adult dentate gyrus have been identified. Gould first demonstrated the influence of adrenal hormones on neuronal production in the adult rat dentate gyrus: glucocorticoids inhibit both neurogenesis and apoptosis (Gould et al., 1991, 1992; Gould and MacEwen, 1993; Cameron and Gould, 1994). Corticosteroids thus slow down the renewal of granule cells in the adult hippocampus. Furthermore, they also regulate migration of newly produced neurons by acting on the proliferation of radial glia (Gould and Cameron, 1996) and on the expression of PSA-NCAM (Rodriguez et al., 1998). This regulation by adrenal steroids implies physiological consequences. For instance, stressful experiences, which are known to increase circulating levels of glucocorticoids, inhibit proliferation of granule cells precursors (Gould et al., 1997, 1998). Thus, chronic stress could result in changes in the structure of the dentate gyrus, raising the possibility that stress alters hippocampal functions through this mechanism (Mac Ewen, 1999; Gould and Tanapat, 1999). Besides, ageing is characterized by increased basal levels of glucocorticoids (Sapolsky, 1992; Lupien et al., 1994), and it has been shown that neurogenesis naturally decreases with age (Kuhn et al., 1996). Recent works showed that reducing corticosteroid levels in aged rats restored the rate of cell proliferation, resulting in an increased number of new granule neurons (Cameron and McKay, 1999; Montaron et al., 1999).

Sex hormones also are involved in neurogenesis regulation. In birds, although HVC volume increases with high levels of circulating androgens (Nottebohm, 1980), sex hormones do not affect cell proliferation (Brown et al., 1993). In contrast, recruitment and survival of newborn neurons as well as neuritic growth and synaptogenesis are stimulated by testosterone (deVoogd and Nottebohm, 1981; deVoogd et al., 1985; Rasika et al., 1994; Doupe, 1994) resulting in sexual dimorphism of this brain structure.

Several recent studies demonstrated the role of estrogens in mammalian neurogenesis regulation. Production of hippocampal and olfactory bulb granule cells vary physiologically during the female rat and meadow vole estral cycle (Tanapat et al., 1999; Smith et al., 2001). It seems that estradiol tends to initially increase, but then subsequently inhibit cell proliferation (Ormerod and Galea, 2001).

Neurotransmitters also play important roles in the regulation of adult neurogenesis in mammals. Regulation of secondary neurogenesis via the activation of NMDA receptors has been the most extensively studied. It has been shown that activation of NMDA receptor inhibits proliferation of granule cell precursors in the dentate gyrus, whereas blockade by MK801, an antagonist of NMDA receptor, results in an increase in cell production in this structure (Cameron et al., 1995). It has been demonstrated that adrenal steroids and NMDA receptor activation regulate neurogenesis through a common pathway (Cameron et al., 1998): glucocorticoid elevation stimulates NMDA secretion in hippocampus (Stein-Behrens et al., 1994), activates NMDA receptors which in turn reduce progenitor cell proliferation. However, progenitor cells do not express NMDA receptor, so the effect observed is most probably indirect (Cameron and Gould, 1996), may be via synthesis of growth factors (Tanapat and Gould, 1997). Anyhow, it is clear that excitatory inputs affect neurogenesis in the hippocampus. Curiously, a recent work reported that a stimulation of mossy fibers sufficient to induce LTP resulted in increased proliferation in the dentate gyrus (Derrick et al., 2000). Thus, it seems that hippocampal neurogenesis can also be regulated by efferent activity.

Contrary to glutamate, serotonine has been shown to enhance neurogenesis, both in dentate gyrus and in SVZ. Indeed, depletion of this neurotransmitter decreases cell production whereas grafting of serotoninergic neurons restores progen-

itor proliferation (Brezun and Daszuta, 1999, 2000).

Moreover, expression of nitric oxide synthase in neurons arborizing close to neural progenitors of the SVZ is consistent with a possible role of nitric oxide in adult neurogenesis modulation (Moreno-Lopez et al., 2000).

Besides their effect on in vitro stem cell proliferation, several growth factors have also been shown to stimulate neurogenesis in vivo. FGF-2 and EGF which can be detected from early stages of development, are still expressed in discrete zones of the adult brain, especially in the granular layer of the dentate gyrus and in the SVZ. Chronic infusion of these growth factors in the lateral ventricle induces an increase in the proliferation of progenitor cells in the SVZ but not in the hippocampus, with a differential effect: FGF-2 induced an augmentation of the number of newborn neurons in the olfactory bulb whereas EGF enhanced the generation of astrocytes in the olfactory bulb (Craig et al., 1996; Kuhn et al., 1997). Peripheral FGF-2 is also able to regulate neurogenesis in the SVZ and in the dentate gyrus of newborn rats, as demonstrated by the effect of subcutaneous injections of FGF-2, suggesting that this growth factor could cross the blood-brain barrier. However, in adult rats, injections of FGF-2 still increased mitotic activity in the SVZ but not anymore in the dentate gyrus (Wagner et al., 1999). By contrast, another growth factor, insulin-like growth factor-1 (IGF-1) has recently been shown to present a stimulatory effect on progenitor cell proliferation in the adult rat dentate gyrus, and to selectively induce neuronal differentiation (Aberg et al., 2000).

4.2. Environmental factors

4.2.1. Seasonal variations

Beyond the internal factors cited above, environmental conditions also play a role in the regulation of secondary neurogenesis. The occurrence of seasonal variations in the proliferation rate of neural precursors was first demonstrated in birds (Alvarez-Buylla et al., 1990; Kirn et al., 1994): peaks of neurogenesis were observed in March and in October, following peaks of neuronal cell death. In *Rana temporaria*, neuron production rate also seems to be influenced by season: the activity of proliferating cell is higher in May/June (after the breeding period) compared to mid-September (Chetverukhin and Polenov, 1993). The mechanisms by which seasons regulate neurogenesis have not yet been elucidated. Temperature and photoperiod have differential effects on lizard postnatal neurogenesis in the medial cortex so that long photoperiod increased the number of proliferating neuroblasts in the ependymal neuroepithelium whereas cold temperature prevented migration of newly produced neurons (Ramirez et al., 1997). In the case of mammals, it is equally possible that photoperiod is partly responsible for these seasonal variations as production and/or survival of neurons increase when day length decreases (Huang et al., 1998).

4.2.2. Sensory inputs

Sensorial stimulation also influences neurogenesis in adults. For instance, in adult insects, environmental quality has been shown to participate in neurogenesis regulation. A recent study demonstrates that crickets reared in enriched sensorial (visual, olfactive, tactile) and social (contacts with congeners) environment exhibit higher proliferation rates in their mushroom bodies with regard to crickets isolated and deprived of most stimuli (Scotto-Lomassese et al., 2000). This effect does not seem to be mediated via hormonal regulation since neurogenesis of JH-deprived insects is still sensitive to these environmental cues. Furthermore, in 'enriched crickets', when one eye and one antennae are lesioned unilaterally, neuroblast proliferation is reduced in the ipsilateral mushroom body as compared to contralateral one (in preparation). These results suggest that the activation of secondary neurogenesis by complex rearing conditions is directly linked to neuronal activity.

Similarly, crayfish individuals isolated in impoverished conditions exhibit a lower rate of neuron proliferation in comparison to their siblings living together in larger areas (Sandeman and Sandeman, 2000).

In adult mice, olfactory deprivation leads to a decrease in the production and survival of olfactory bulb neurons (Corotto et al., 1994). Conversely, enrichment of the environment leads to a larger number of granule cells in hippocampus due to preferential neuronal differentiation together with increased survival of newborn neurons (Kempermann et al., 1997, 1998). Several studies demonstrated that the quality of the environment could affect the expression of growth factors such as NGF, GDNF, BDNF, and the phosphorylation of

the cAMP response element binding protein (CREB) (Young et al., 1999; Pham et al., 1999), suggesting that the effect of environment on neurogenesis could be mediated by such mechanisms. For instance, in male canaries, BDNF expression in the HVC is proportional to singing activity, and parallely survival of new HVC neurons is greater in singing birds compared to non-singing birds (Li et al., 2000). Furthermore, it has also been shown that birds or rodents trained for spatial exercises involving hippocampic formation present a higher recruitment and an improved survival of newborn neurons in the dentate gyrus as compared to naive animals (Patel et al., 1997; Gould et al., 1999b; Ambrogini et al., 2000). Similarly, voluntary physical activity in a running wheel enhances the number of new hippocampal neurons in adult mice (van Praag et al., 1999a).

5. Functional implications of adult neurogenesis

The reasons why progenitor cells persist in the adult central nervous system and give rise to new neurons in some particular brain structures remain unclear, and this question is of great interest. When the first evidences of proliferative neuroblasts in adult rodent brain were published (Kaplan and Hinds, 1977), it was then thought that this persistent neurogenesis was only a vestige of development without necessarily functional importance. Since, many other studies have demonstrated the occurrence of adult neurogenesis in insects, birds, tree shrews, marmosets, macaques and humans (Cayre et al., 1994; Goldman and Nottebohm, 1983; Gould et al., 1997, 1998; Kornack and Rakic, 1999; Eriksson et al., 1998). The evolutionary conservation of this process suggests that it is of fundamental biological importance. Newly generated granule cells differentiate and form new synapses rapidly (Hastings and Gould, 1999; Markakis and Gage, 1999). They show distinct morphological and electrophysiological properties as compared to mature granule cells (Liu et al., 2000), present a lower threshold for induction of LTP and display robust LTP (Wang et al., 2000). Furthermore, the fact that secondary neurogenesis takes place in structures involved in learning and memory raises the possibility that newborn neurons could participate in mnemonic processes and thus improve behavioral adaptation of the animal to its environment. Several types of experiments have been undertaken to support this hypothesis, and convincing correlations have been discovered between neurogenesis and mnemonic performances although no direct evidence is yet available (Fuchs and Gould, 2000).

5.1. In invertebrates

In crickets, JH, which stimulates neurogenesis in the mushroom bodies of the adult, is also necessary for the expression of oviposition behavior in the female: females deprived of JH before the imaginal moult will never oviposit, whereas JH injection induces the apparition of this behavior, after a 2-to-3 days delay. By contrast, once the egg-laying behavior is set, removal of JH does not prevent its expression (Renucci et al., 1992). We thus investigated whether JH-induced neurogenesis was responsible for the establishment of oviposition behavior in the adult female. Mushroom body neurogenesis was inhibited using α-difluoromethylornithine (DFMO), a specific and irreversible inhibitor of putrescine biosynthesis. In DFMO-treated females, the expression of egg-laying behavior was delayed, and the oviposition frequency was drastically reduced (Cayre et al., 1996b). Another approach intending to trigger mushroom body neuroblast degeneration in adults via the administration of hydroxyurea, an antimitotic drug, is actually under investigation. Preliminary results show that hydroxyurea-treated females present an inhibition of neuroblast proliferation of 75% as compared to control females, and either do not oviposit at all, or express only very weakly the oviposition behavior. However, it seems that locomotor activity of treated females is also diminished, raising the possibility of general toxic rather than specific effect of the drug. Further work will be needed to determine the specific part of neurogenesis reduction in egg-laying behavior inhibition.

5.2. In vertebrates

It is in singing birds that evidence for a functional role of newborn neurons are most convincing. For instance, in canaries, song is specific to males, who modify their repertoire, by listening to congeners, and by adding, dropping or altering song syllables. Some studies showed that HVC volume is greater in males than in females, but also increases proportionally to song virtuosity. Furthermore, seasonal variations in the production

of new neurons correlate with acquisition of new syllables: song stability is maximal when canaries breed and recruitment of new neurons is at its lowest (Kirn et al., 1994). It has been hypothesized that neuronal replacement in HVC provides a cellular basis for the song plasticity in adult canaries (Alvarez-Buylla et al., 1992; Kirn and Nottebohm, 1993). Recently, Scharff et al. (2000) dissected the contribution of different sets of HVC projection neurons to adult song behavior. They demonstrated that targeted destruction of RA-projecting neurons resulted in highly deteriorated song, and that song impairment recovered partially or completely after 2 months, coincidentally with the upregulation of neuronal replacement.

In other birds, as well as in wild rodents, natural behaviors of storing and retrieval of food involving hippocampus, is a function of the seasons. In such cases, hippocampus volumes vary accordingly to the task accomplished. Furthermore, these species exhibit better performances in spatial learning tasks than non-food storing species (Lee et al., 1998). In laboratory conditions, learning abilities of rats and mice (tested in watermaze or Hebb–Williams maze) seems directly correlated to proliferation rates in the subgranular layer of dentate gyrus. Hormonal and experiential factors that enhance neuron production (estrogens, running, environment-enrichment...) are associated with improved performance in hippocampal learning tasks (Kempermann et al., 1997; Luine et al., 1998; van Praag et al., 1999a). It has even been shown that running selectively enhances dentate gyrus LTP (van Praag et al., 1999b). Conversely, conditions that inhibit neurogenesis (adrenal steroids, aging, stress) are associated with diminished performances in hippocampal-dependent tasks (Bodnoff et al., 1995; Gallagher and Pelleymounter, 1988; Krugers et al., 1997). Another study showed that behavioral trait of reactivity, a character hippocampus-dependent, is related to dentate gyrus neurogenesis (Lemaire et al., 1999). Recently, Shors et al. (2001), using an antimitotic drug to inhibit neurogenesis in the dentate gyrus, demonstrated that treated rats exhibited an impaired hippocampal-dependent trace conditioning which was reversed after the end of drug administration.

Concerning neurogenesis in the SVZ, producing new olfactory bulb interneurons, a recent novating work demonstrated the importance of newly generated neurons for odor discrimination but not for general olfactory functions (Gheusi et al., 2000).

6. Concluding remarks

From the above data, it appears that similar processes are underlying neurogenesis in the adult brain of invertebrates and vertebrates.

Stem- or progenitor-cells are still present in the central nervous system of adults. However, it must be underlined that progenitor cell repartition differs in vertebrates and insects. Whereas progenitor cells are scattered along the border of the SVZ or the granular layer of hippocampus in mammals, the persistent neuroblasts of crickets are arranged in a cluster located at the apex of mushroom body cortex, offering a better opportunity to consider the feasibility of their selective destruction. In invertebrates, as in vertebrates, internal factors and especially hormones and neurotransmitters play important roles in the regulation of adult neurogenesis. Similarly, environmental factors are involved in the modulation of secondary neurogenesis.

It is worth noting that, in both vertebrates and invertebrates, secondary neurogenesis occurs in important brain structures exhibiting a high degree of structural plasticity and displaying remarkable analogies, as they receive multiple sensory information and play a central role in learning and memory processes. Similarities between vertebrate hippocampus and insect mushroom bodies are particularly striking. Both structures are regulated by networks of oscillatory interneurons synchronized by inhibitory GABAergic retrocontrols (Laurent and Davidovitz, 1994; Buszaki, 1997), and exhibit the phenomenon of long-term potentiation and long-term depression (Bliss and Collingbridge, 1997; Oleskevich et al., 1997).

Although the functional role of the newly formed neurons remains still questionable, the recent discovery of neurogenesis in the adult human hippocampus (Eriksson et al., 1998) has definitely ruled out the concept of the immutability of adult brain structures. Moreover, the possibility to isolate cell lines of stem cells opens new perspectives in medical research for treatment of brain trauma or neurodegenerative diseases. All these findings are giving hope that structural brain repair through induced neurogenesis will possibly become of clinical use.

7. Uncited references

Bliss and Collingridge, 1993; Buzsaki, 1997; Gould and McEwen, 1993; Laurent and Davidowitz, 1994; McEwen, 1999; Ormero and Galea, 2001

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