ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2004, 64: 189-200

Serotonin and neurogenesis in the hippocampal dentate gyrus of adult mammals

Rouzanna L. Djavadian

Department of Molecular and Cellular Neurobiology, Nencki Institute of Experimental Biology, 3 Pasteur St., 02-093 Warsaw, Poland, Email: r.djavadian@nencki.gov.pl

Review

Abstract. It is well documented that in mammals new neurons are generated in the dentate gyrus (DG) and integrated into hippocampal circuits throughout their life. However, functions of these newly generated cells are still hotly debated. One of the important factors that may influence the rate of DG neurogenesis is serotonin. Apart from being a neurotransmitter and neuromodulator it plays many other roles in the central nervous system, including the role of a trophic factor influencing functional state of neurons. In this review I discuss the changing views on adult hippocampal neurogenesis then briefly describe the anatomy and function of the hippocampus, focusing on its serotonergic innervation and receptors. Further, the possible role of serotonin and the newly generated DG neurons in hippocampus-dependent memory is discussed. Finally mechanisms by which serotonin and its receptors influence neurogenesis in the adult DG are summarized and hypotheses linking the decreased rate of DG neurogenesis with mechanisms of depression are discussed.

Key words: serotonin, neurogenesis, dentate gyrus, hippocampus, memory, stress, depression, antidepressants

CHANGING VIEWS ON ADULT NEUROGENESIS

At the beginning of the 20th century an overwhelming majority of prominent neuroanatomists and neurophysiologists hold the opinion that "after birth no new neurons may be added to the mammalian central nervous system". That opinion, transformed into a theory (or law), was later uphold for half a century, in spite of some early evidence questioning it (Hamilton 1901, Sugita 1918). The main reason for which His (1904), Ramon y Cajal (1913) and other leading scientists refused to accept the possibility that new neurons may be generated and incorporated into the brains of adult vertebrates was the lack of methods allowing for tracing the newly generated brain cells long enough so they would migrate into their final places (frequently far away from the place of generation) and differentiate into anatomically distinguishable neurons or glia.

In 1959 Sidman et al. (1959) invented the method of labeling dividing cells with tritiated thymidine. When incorporated into the newly synthesized DNA during the S phase of cell division, the thymidine may be detected weeks or months later with autoradiography made on histological sections. Since 1962, Altman used that method for timing generation of various cellular populations in the developing brain, from the fetal stage to adult. His investigations showed that in two structures of the rodent brain, namely the subventricular zone of the lateral ventricles (SVZ) and the dentate gyrus of hippocampus (DG) neurogenesis continues throughout life (Altman 1962, 1969, Altman and Das 1965). For the next twenty years these findings of Altman were largely ignored, as they contradicted the well established "law".

The next important breakthrough came from investigations of learning mechanisms in the song birds. These investigations, conducted in the laboratory of Nottebohm, showed that newly generated brain cells migrated from the vicinity of lateral ventricles to several brain nuclei, especially to the high vocal center that is responsible for learning the song sequence, and there they differentiated into neurons (Goldman and Nottebohm 1983, Nottebohm 1985). Generation of these new neurons was seasonal, coinciding with the time these birds were singing in their territories, and they were necessary for learning the song or modifying it. Other investigations showed that in some other species of birds seasonal formation of new spatial memory traces was accompanied by increased neurogenesis in their cortical structures that are equivalent to the mammalian hippocampus, and in fact depended on that neurogenesis (Li et al. 2000, Nottebohm 2002).

Although the results of investigations on birds for the first time ascribed specific functions to the adult neurogenesis in the DG, they did not draw broader attention either, until Eriksson et al. (1998) showed neurogenesis in the dentate gyrus of adult humans. That finally broke the "dogma of no adult neurogenesis" (Gross 2000). Eriksson used the bromodeoxyuridine (BrdU), another marker of the dividing cells that was introduced by Gratzner (1982) and used afterwards by several other investigators to show neurogenesis in the adult mammalian brain (Alvarez-Buylla and Lois 1995, Kaplan 1983, Miller and Nowakowski 1988, Skup et al. 1993). In the following years many investigators confirmed earlier results and showed that permanent generation of new neurons in these two brain structures is a common mammalian feature, present in rodents, primates, macroscelids, insectivores and carnivores (Bialoskorska et al. 2001, Gould et al. 1998, for review see Gage 2000). The life-long presence of proliferation in the DG was showed in all investigated mammalian species except of the Sorex shrews (Bialoskorska et al. 2001). The majority of newly generated cells differentiated into the DG granular neurons (Gage 2000, Gould et al. 1999a, Stanfield and Trice 1988) that integrated into hippocampal circuitries (Van Praag et al. 2002).

Cells generated in the SVZ and migrating to the olfactory bulb (OB) were also found in all investigated mammals. In the OB they differentiate into GABA-ergic and dopaminergic inhibitory interneurons that improve discrimination between odors (Betarbet et al. 1996, Gheusi et al. 2000). The main external factor influencing the rate of proliferation in the SVZ is the activity of olfactory receptors (Corotto et al. 1994). In humans new cells do not migrate from SVZ, but are quickly eliminated by apoptosis in the rostral migratory stream (RMS) (Sanai et al. 2004). Proliferation, survival and differentiation of the SVZ-generated neurons may be regulated differently than those generated in the DG and will not be discussed in this review.

There are also some data showing that in mice new neurons may be generated in the SVZ of the brain aqueduct and later migrate to the substantia nigra (Zhao et al. 2003), and that in the macaque monkeys some neurons generated in the SVZ of the lateral ventricles may migrate to the frontal cortex (Gould et al. 1999b).

DENTATE GYRUS AS A PART OF THE HIPPOCAMPAL FORMATION

Hippocampal formation is a part of the allocortical structures. Cytoarchitectonically the formation is divided into four areas: dentate gyrus (DG), hippocampus (or cornu ammonis, divided into areas CA1, CA2 and CA3), the subicular complex (subiculum, presubiculum and parasubiculum) and the entorhinal cortex. All parts of the hippocampal formation are the layered structures. DG is built of three main layers: molecular, granule cell and polymorphic cell (or hilar). Granule cells, the main type of the DG neurons, are located in the second layer where they are densely packed, without glial cells intercalated among them. The cone-shaped dendritic trees of granule cells are directed towards the molecular layer that contains also dendrites of the basket and polymorphic cells, axonal arbors and small stellate and chandelier cells (Claiborne et al. 1990). The majority of the non-granular types of neurons (the chandelier, basket, mossy, multipolar and fusiform cells) are GABA-ergic and therefore inhibitory interneurons.

The majority of hippocampal areas are connected by unidirectional projections, forming a loop through which information is processed within the hippocampus. A series of these projections starts with the perforant path, formed by axons of the entorhinal cortex neurons that project to DG. This is the main pathway through which sensory information enters hippocampus and therefore DG plays a key role in selecting the incoming information and forming memory traces (Steward 1976, Witter 1993). Axons of the DG granule cells, called mossy fibers (Ramon y Cajal 1911), terminate on pyramidal cells of the fields CA3 and CA2 (Ribak et al. 1985). Then axons of the CA3 and CA2 pyramidal neurons (called Schaffer collaterals) reach the CA1 field, and axons of the CA1 neurons end in the subiculum. Starting from the subiculum, further projections are becoming bilateral. The entorhinal cortex projects also directly to CA3, CA2, CA1 and subiculum (for detailed descriptions of the hippocampal connections cf. Amaral and Witter 1995). Therefore, the most important information reaching hippocampus originates in the neocortex, is sent to the entorhinal cortex and then to DG, elaborated in the hippocampal circuits and distributed again to the neocortex, first of all to the cingulate cortex.

There are also several subcortical projections to DG. Among them are those from the septal nuclei, hypothalamic supramammillary region, anterior and central thalamic nuclei, amygdala, locus coeruleus and raphe nuclei. The majority of septal axons that heavily innervate DG terminate in the polymorphic and molecular layers. This input is cholinergic and GABA-ergic (Amaral and Kurz 1985, Freund and Antal 1988). Axons of large neurons of the supramammillary nucleus terminate densely in the upper part of the granule cell layer and scarcely in the polymorphic and molecular layers (Haglund et al. 1984). Afferents from amygdala, midline thalamic nuclei and hypothalamus end in the area CA1 (Amaral and Witter 1995) and form the link between emotions-related structures and hippocampal circuits. Only the polymorphic cell layer gets noradrenergic innervation from the locus coeruleus (Haring and Davis 1983, 1985). Serotonergic innervation of the hippocampal formation is dense and highly organized (Moore and Halaris 1975, Tork 1985).

SEROTONERGIC INNERVATION AND SEROTONERGIC RECEPTORS OF THE DENTATE GYRUS

Serotonin is an evolutionary ancient signaling molecule that plays many roles in various animal species and various tissues (Turlejski 1996, Whitaker-Azmitia 1991). In the central nervous system it is a modulatory neurotransmitter participating in regulation of many important brain functions like thermoregulation (Feldberg and Myers 1964), sleep (Jouvet 1967), aggression (Sheard 1969), feeding (Lucki 1992). Disturbed serotonergic signaling is an important mechanism of such psychopathological states as anxiety (Chopin and Briley 1987), depression (Pinder and Wieringa 1993), eating disorders (Leibowitz and Shor-Posner 1986).

In the brain of mammals serotonin is produced by neurons located mainly in the brainstem raphe nuclei. Fibers from these nuclei extend to the brain through the medial forebrain bundle (mfb) (Azmitia and Segal 1978, Parent et al. 1981) and then join all main fiber bundles in the forebrain. They terminate in virtually all brain structures, but the structures with the densest serotonergic innervation are: olfactory bulb, hypothalamus, septum, striatum, thalamus, caudoputamen, hippocampus and cerebral cortex (Jacobs and Azmitia 1992, Leger et al. 2001).

Serotonergic innervation of the hippocampal areas is variable (Bjarkam et al. 2003, Moore and Halaris 1975, Vertes et al. 1999). DG has a very dense plexus of serotonergic fibers in the molecular and hilar layers, and

especially in the subgranular zone, where it synapses preferentially on interneurons (Halasy and Somogyi 1993, Tork 1985). There are two different morphological types of the serotonergic fibers: fine and beaded axons (Kosofsky and Molliver 1987, Tork 1985). Fine axons (less than 1 μm in diameter) with small fusiform or granular varicosities originate from the dorsal raphe nucleus (DR), enter DG through the entorhinal cortex and project mainly to the molecular layer. The beaded axons, having large spherical varicosities, originate from the median raphe nucleus (MR), extend through the cingulum bundle and fornix and project to the hilar layer (Azmitia and Segal 1978). The serotonergic projection from MR is denser than the DR projection. Haring (1991) showed that after the MR lesion serotonergic fibers from DR may sprout to the hilar layer, where they may change their morphology from fine to beaded axons.

Serotonin activates fifteen different receptors that are classified into seven groups and almost all of these receptors are expressed in the DG (Clemett et al. 2000, Djavadian et al. 1999, El Mestikawy et al. 1989, Kinsey et al. 2001, Tecott et al. 1993, Vilaro et al. 1996). The 5-HT_1 receptors (with subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}) are coupled to the G_i protein. Their activation decreases the activity of adenylyl cyclase and therefore decreases the rate of formation of cAMP. One of the indirect results of activation of these receptors is the increased conductance of cell membrane for the K^+ ions. Activation of the 5-HT_4, 5-HT_6 and 5-HT_7 receptors that are coupled to the G_s proteins has the opposite effect: they increase the rate of cAMP formation and decrease the K^+ conductance (Raymond et al. 2001, Thomas et al. 2000). The 5-HT_2 receptors (with subtypes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}) coupled to the G_q proteins activate phospholipase C (PLC), increasing the rate of formation of inositol triphosphate (IP_3). The 5-HT_3 receptors (subtypes 5-HT_{3A} and 5-HT_{3B}) are ligand-gated Na^+ ion channels and their activation results in depolarization of neurons (Barnes and Sharp 1999). The intracellular transduction pathway of the 5-HT_5 receptor group (subtypes 5-HT_{5A} and 5-HT_{5B}) is not clear yet.

Depending on what subset of the serotonergic receptors has been activated, neurons of the DG may be either depolarized by serotonin and therefore increasing their excitability or hyperpolarized and inhibited. However, one of the main results of activation of all those serotonergic receptors that are coupled to the G proteins (like the $5HT_1$ group) is the change in the intracellular signaling that changes the metabolic state of the cell and expression of various genes. Results of serotonergic activation may also depend on the type of cell, and in the progenitor cells of the central nervous system serotonergic activation may induce mitosis (Malberg et al. 2000). Therefore, induction of cells' divisions and increase of the rate of proliferation are within the broad scope of possible actions of serotonin.

SEROTONIN AND NEUROGENESIS IN THE DENTATE GYRUS

In adult mammals cells generated in the subgranular layer of DG migrate to the granule cell layer of that gyrus and are incorporated there (Gage 2000, Jacobs 2002, Stanfield and Trice 1988). These new cells mature, grow dendrites into the molecular layer of DG and send axons into the mossy fibers tract, establishing synaptic contacts with pyramidal neurons of the area CA3, that are typical for the DG granule cells. In mice and rats numbers of the newly generated DG neurons vary from 1,000 to 3,000 per day. As there are between 1 and 2 millions of the DG neurons in these species and the numbers of these neurons do not increase with age, therefore every day about one in a thousand of the DG neurons is replaced, which means that a substantial proportion of the DG granule cells (10-20%) are exchanged during the lifespan of an animal (Jacobs 2002).

Several factors may decrease the rate of generation of these new cells in the adult DG. Some of the better known factors are glucocorticoids (Cameron et al. 1993) and activation of the glutamate NMDA receptors (Cameron et al. 1995). Cholinergic deafferentation of the hippocampal formation by transection of the fimbria-fornix resulted in the increased rate of proliferations in the DG, which shows that acetylcholine is also decreasing the rate of neurogenesis. Treatment of the lesioned animals with neurotrophic factors (NGF) or basic fibroblast growth factor (bFGF) after that lesion did not change the rate of proliferation (Skup et al. 1993). The epidermal growth factor (EGF) (Reynolds and Weiss 1992), basic fibroblast growth factor (bFGF) (Tao et al. 1996) and voluntary exercise in the running wheel that is increasing the level of neurotrophins (Van Praag et al. 1999) all increase the rate of proliferation in the DG.

One of the most important factors regulating proliferation in the DG is serotonin. Brezun and Daszuta (1999)

found, that depletion of serotonin in the brains of adult rats decreased the numbers of the BrdU-labeled (newly generated) neurons in both SVZ and DG. These authors were injecting a serotonergic neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT), into the raphe nuclei causing a massive destruction of the serotonergic axons and loss of some of the raphe neurons. Five to seven days after this serotonergic lesion, numbers of the BrdU-labeled nuclei in the DG decreased. Full depletion of the serotonergic innervation of DG lasted for one month and during that time the rate of generation was reduced by about 60%. During the second month DG was gradually reinnervated by sprouting serotonergic axons and starting from the third month there was no difference between the control and 5,7-DHT injected animals in both serotonergic innervation of the DG and the numbers of newly generated cells in that structure (Brezun and Daszuta 2000). Injections of another neurotoxin, parachlorophenylalanine (PCPA) that inhibits 5-HT synthesis without destroying the serotonergic neurons or axons again suppressed the DG neurogenesis, proving that the main factor that slowed down the rate of neurogenesis was the reduced level of serotonin, and not other variables introduced by destruction of the serotonergic axons (Brezun and Daszuta 1999). Predictably, increased level of serotonin resulted in the increased rate of proliferation in the DG (Malberg et al. 2000, see below for broader description). Therefore, in spite of the large number of serotonergic receptors expressed in the DG and their possibly contradictory actions, influence of serotonin on neurogenesis in the hippocampus is very consistent: its depletion reduces, whereas its increased level increases the rate of neurogenesis in the DG.

Out of the numerous serotonergic receptors, the 5-HT_{1A} receptor is the one most likely involved in regulation of neurogenesis in the DG. Direct involvement of these receptors in cells' proliferation has been shown in the *in vitro* experiments. When fibroblasts transfected with the 5-HT_{1A} receptors were cultured in a medium containing the 5-HT_{1A} agonist (8-OH-DPAT), the rate of their divisions increased (Varrault et al. 1992). Akbari et al. (1994) investigated the influence of signaling through that receptor on the developmental neurogenesis. They found that reduction of the level of serotonin in the rat fetuses induced by treatment of the pregnant dams with cocaine resulted in microencephaly in the newborn pups and that the thickness of their cerebral cortex was significantly reduced. Five days of postnatal treatment of these pups with a 5-HT_{1A} agonist, ipsapirone, increased the thickness of their cortex. Authors postulate, that ipsapirone stimulated generation and migration of astrocytes expressing the S-100β trophic factor and its release stimulated growth of dendrites, allowing for recovery of the cortical thickness. However, it is not clear if in these pups the numbers of cortical neurons were reduced due to the fetal serotonergic deprivation. In the adult rats three different antagonists of the 5-HT_{1A} postsynaptic receptors: NAN-190, *p*-MPPI and WAY-100635 reduced the numbers of newly generated DG cells by about 30% (Radley and Jacobs 2002). Injections of the 5-HT_{1A} agonists had the opposite effect: the numbers of the BrdU labeled cells in the rat DG increased (Santarelli et al. 2003). Activation of the 5-HT_{2A} and 5-HT_{2C} receptors also increased neurogenesis in the DG, while agonists of the 5-HT_{1B} receptors increased the neurogenesis only after serotonergic depletion (Banasr et al. 2004).

Other types of serotoninergic receptors that may be involved in mediating the effects of serotonin on proliferation in the DG are the 5-HT_4, 5-HT_6 and 5-HT_7 receptors. All of them, when activated, trigger the cAMP cascade. One of the results of increased signaling in that pathway is triggering expression of the cAMP response element binding protein (CREB). The cAMP-CREB cascade may then increase expression of BDNF. BDNF does not directly change the rate of neurogenesis in the DG, but it may increase the release of serotonin (Siuciak et al. 1996) and that in turn may stimulate neurogenesis through increased activation of the 5-HT_{1A} receptors (Duman et al. 2001).

Activation of the NMDA receptors is another possible cause of the decrease of neurogenesis in DG after serotonergic depletion. Normally, serotonin hyperpolarizes granule cells and possibly also the progenitor cells placed nearby. Therefore, depletion of serotonin may result in their depolarization and hyperexcitability that activates the NMDA receptors (Cameron et al. 1995). Increased activation of these receptors causes calcium influx into the cell that influences many intracellular processes. Such activation is also known to decrease the rate of proliferation in the DG (Krugers et al. 1993, Moghaddam et al. 1994).

HYPOTHESES CONCERNING THE ROLE OF DG NEUROGENESIS IN LEARNING AND MEMORY

The main function of the hippocampus is its participation in formation, retrieval and reworking of the declarative memory (Scoville and Milner 1957). One of

the possible mechanisms of learning or relearning tasks demanding the use of spatial memory is the exchange of neurons in the DG (Nottebohm 2002), and therefore it is not surprising that many studies have been devoted to link the learning and memory functions to neurogenesis in the hippocampal DG (for review cf. Suzuki and Clayton 2000). However, experiments investigating relations of the hippocampus-dependent learning in the Morris water maze task and proliferation in the DG brought contradictory results.

An early paper of Van Praag et al. (1999) did not find any coincidence of the process of hippocampus-dependent learning with the numbers of BrdU labeled (i.e., newly generated) cells. Contrary to that result, Lemaire et al. (2000) found an increase in the rate of proliferation in DG in the same task. This inconsistence could be ascribed to different timing of the BrdU injections and underestimation of the rate of proliferation by Van Praag and colleagues (1999). If increased numbers of newly generated cells improve learning, then downregulation of neurogenesis should impair it. Life-long reduction of the DG neurogenesis in rats due to prenatal stress produced learning deficits (Lemaire et al. 2000). Shors et al. (2001) showed that downregulation of neurogenesis impaired hippocampal-dependent trace conditioning while it did not affect hippocampal-independent memory. Neurogenesis decreases with age (Gould et al. 1999c, Kuhn et al. 1996) and this decrease could be the cause of memory impairment and cognitive decline in the old age (Bizon and Gallagher 2003). However, recently the correlation of spatial learning abilities and neurogenesis in the aged rats was questioned (Merrill et al. 2003).

Learning and behavior are complex phenomena where various factors may interact with each other. In the Morris water task there is learning of the position of the platform, stress induced by swimming in lukewarm water and physical activity necessary for swimming. It is not clear to what extent these factors interact and not always possible to separate them. Stress is known to reduce proliferation in the DG (Gould et al. 1998), while voluntary physical activity in the running wheel increased not only proliferation but also survival of these new cells (Van Praag et al. 1999). Different subpopulations of the DG progenitors may respond differently to the same stimuli (Kronenberg et al. 2003). Running is correlated with the hippocampal theta rhythm (Czurko et al. 1999) and long-lasting locomotor activity may change serotonergic transmission, among others *via* the 5-HT_3 receptor (Staubli and Xu 1995). This in turn alters the theta-rhythm frequency, enhancing long-term potentiation and improving memory. In the same time increased level of serotonin upregulates proliferation in the DG directly. Therefore, the debate about relation of the hippocampus-dependent learning to the adult neurogenesis in DG continues, but there are many problems and doubts about such causal relation (Gould and Gross 2002, Rakic 2002).

Another hypothesis links DG neurogenesis to the environmental enrichment and reactivity to novelty. Investigations of the influence of environmental enrichment on behavior of animals showed that enrichment improved learning and memory and in the same time increased neurogenesis in the DG. Mice living in the enriched cages were more efficient in finding platform in the Morris water maze task than the control mice living in the standard housing cages (Kempermann et al. 1997). Similarly, rats living under enriched conditions when tested on a different spatial memory task (T-maze) learned better than the control rats housed in cages with a running wheel (Bernstein 1973). Animals living in the enriched environment showed also increased synaptogenesis (Globus et al. 1973) and enhanced expression of the 5-HT_{1A} receptor, which could influence the rate of proliferation (Rasmuson et al. 1998). However, rats that were highly reactive to novelty had depressed proliferation in the DG, due to the stress induced by novelty that increased the level of corticosterone (Lemaire et al. 1999).

DECREASE OF THE DG NEUROGENESIS AS A POSSIBLE MECHANISM OF DEPRESSION

Hippocampal inputs from hypothalamus, anterior and middle thalamic nuclei and the amygdala and the hippocampal output from subiculum to the cingulate cortex, form a strong basis for participation of the hippocampal formation in the emotions-related behavior. Several recent papers postulate a role of the hippocampal formation in regulation of the affective states, reaction to unpleasant emotions and Pavlovian fear memory (Lane et al. 1997, Phillips et al. 2003, Seidenbecher et al. 2003).

Stress is the most significant environmental factor in depression. It is also known to suppress neurogenesis in the DG through several mechanisms (Benninghoff et al. 2002, Cameron et al. 1995, Gould et al. 1992, Jacobs et al. 2000). There are many pathways on which stress may negatively influence neurogenesis. Stressful experi-

ences activate the hypothalamic-pituitary-adrenal axis increasing release of the corticoid hormones. The steroid stress hormones, especially glucocorticoids, reduce the rate of proliferation in the DG, independent of the level of serotonin (Cameron et al. 1993). However, the DG progenitor cells do not express glucocorticoid receptors and therefore the mechanism of the stress-induced reduction of the rate of neurogenesis must depend on some indirect influences. First, glucocorticoids are known to decrease the activity of serotonergic receptors (Lopez et al. 1998) and this may decrease the rate of proliferation in the DG. What more, stress activates also the glutamatergic excitatory input to the hippocampus and the NMDA receptors that are known to inhibit hippocampal proliferation (Bartanusz et al. 1995, Krugers et al. 1993, Moghaddam et al. 1994). But a very important component of the stress syndrome is the decrease of serotonin level (Koprowska et al. 2002) that may directly decrease the DG neurogenesis.

Jacobs et al. (2000) postulate, that the decrease of neurogenesis itself may be an important cause of depression. Recent MRI imaging studies of the brains of depressed patients showed neuroanatomical changes in their hippocampi. In patients suffering from major depression both the volume of the whole hippocampus and volume of its gray matter were reduced (Bremner et al. 2000, Sheline 1999). According to the neurogenetic hypothesis, these changes at least partially depend on reduction of the rate of proliferation in the DG, and therefore an increase of the rate of generation of new DG cells should reverse structural changes in the hippocampus and alleviate depression.

This hypothesis was tested on several recently introduced animal models of human depression. Using the model of psychosocial stress in the adult tree shrews (*Tupaia belangeri*), where the presence of the dominant animal influences the subordinate animal, Czeh et al. (2001) showed that that stress decreased the hippocampal volume and reduced proliferation rate in the DG by 33%. They found, that the decrease of hippocampal volume depended mainly on the involution of dendritic trees of the CA3 pyramidal neurons. Measurements of the volume of granule cell layer showed that reduced neurogenesis in the DG did not contribute to reduction of hippocampal volume. In another model of depression adult rats were exposed to an odor of a predator. As a result, the rate of proliferation in their DG decreased (Tanapat et al. 2001). Therefore, in this model relations of the changes in the DG proliferation rate to the reduced hippocampal volume are dubious. What more, the rate of DG proliferation does not correlate with the development of learned helplessness in the rats that is a model of major depression (Vollmayer et al. 2003).

It is well established that a majority of the antidepressant drugs that are used in the treatment of depressive illness increase the level of monoamines, most of all the level of serotonin and noradrenalin. Chronic (i.e., lasting 14-28 days) administration of antidepressants, like tranylcypromine (monoamine oxidase inhibitor), fluoxetine (selective serotonin reuptake inhibitor) or reboxetine (selective norepinephrine reuptake inhibitor) in the rats increased the numbers of BrdU-labeled nuclei in the DG by 20-40% in comparison to control animals. Phenotype of these BrdU-labeled cells was determined 28 days after the BrdU injection, when the cells fully differentiated. At that time they were located in the granule cell layer of the DG and 75% of them were neurons with the granule cell morphology. In contrast, acute (1 to 5 days) treatment with antidepressants did not change the rate of proliferation in the rats' DG (Malberg et al. 2000).

It is possible that the long-lasting antidepressant treatment increases neurogenesis by activation of the 5-HT_{1A} receptors (Haddjeri et al. 1998). This hypothesis was verified on the 5-HT_{1A} knockout mice (Santarelli et al. 2003). In the normal (wild-type) mice administration of the 5-HT_{1A} agonist (8-OH-DPAT) or fluoxetine for 28 days before performing the novelty-suppressed feeding test simultaneously decreased the latency to start feeding and increased the numbers of BrdU-positive cells by 60%, whereas in the knockout mice the same treatment did not influence either the latency or the rate of proliferation. However, in the knockout mice imipramine that activates a different (noradrenergic) pathway still increased the rate of neurogenesis after long-lasting treatment (11 or 28 days). The increased level of serotonin due to the antidepressant treatment may also increase the release of BDNF, and this may indirectly stimulate neurogenesis in the DG (Duman et al. 2001). Increasing the level of serotonin, antidepressant treatment activates all serotonergic receptors. Little is known about involvement of other serotonergic receptors in both antidepressant and pro-mitotic effects of serotonin, but the 5-HT_4, 5-HT_6 and 5-HT_7 types may likely mediate some effects.

Therefore, various antidepressant treatments may stimulate several independent pathways influencing neurogenesis in the DG and serotonin level in the brain

is a prominent, but not exclusive factor in both antidepressant treatment and neurogenesis in the DG.

CONCLUSIONS

It is well documented that depletion of serotonin in the brain results in suppression of neurogenesis in the adult hippocampal DG, whereas elevation of its level increases the rate of neurogenesis. However, serotonin is only one of many factors regulating and controlling neurogenesis.

The majority of the antidepressant drugs increase the level of serotonin, and therefore one of their effects could be the increase of the rate of neurogenesis in DG. Some hypotheses link depression to the deficit of neurogenesis in DG and postulate that the increase in the rate of neurogenesis plays an important role in the mood-stabilization effect of the antidepressant drugs. However, there are few facts supporting this hypothesis, except for the parallel dynamics of the antidepressant action and neurogenesis. Another hypothesis, postulating crucial role of the DG neurogenesis in formation or change of the spatial memory in mammals becomes gradually less and less compatible with the results of the majority of experiments.

Therefore, as yet we are not able to ascribe a definite role to the adult neurogenesis in the DG, which means that in spite of many investigations we are missing a very important point. The knowledge of the functions and behavior that depend on neurogenesis in the DG and the influence of the new neurons on these functions is crucial for better understanding of the functions of hippocampal formation. It is also crucial to understand better the role of serotonin and its various receptors in hippocampal functions and pathologies. Such knowledge may also open new perspectives for treatment of human psychopathological diseases.

ACKNOWLEDGEMENT

Supported by the grant no. 0408/P05/2002/22 of the Polish State Committee for Scientific Research (KBN).

REFERENCES

Akbari HM, Whitaker-Azmitia PM, Azmitia EC (1994) Prenatal cocaine decreases the trophic factor S-100β and induced microcephaly: reversal by postnatal 5-HT_{1A} receptor agonist. Neurosci Lett 170: 141-144.

Amaral DG, Kurz J (1985) An analysis of the origins of the cholinergic and noncholinergic septal projections to the hippocampal formation of the rat. J Comp Neurol 240: 37-59.

Amaral DG, Witter MP (1995) Hippocampal formation. In: The rat nervous system (Ed. G. Paxinos). Adademic Press, San Diego, London, p. 443-494.

Altman J (1962) Are new neurons formed in the brains of adult mammals? Science 135: 1127-1128.

Altman J (1969) Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 137: 433-458.

Altman J, Das GD (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 124: 319-335.

Alvarez-Buylla A, Lois C (1995) Neuronal stem cells in the brain of adult vertebrates. Stem Cells 13: 263-272.

Azmitia EC, Segal M (1978) An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J Comp Neurol 179: 641-667.

Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 29: 450-460.

Barnes NM, Sharp T (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38: 1083-1152.

Bartanusz V, Aubry J-M, Pagliusi S, Jezova D, Baffi J, Kiss JZ (1995) Stress-induced changes in messenger RNA levels of N-methyl-D-aspartate and AMPA receptor subunits in selected regions of the rat hippocampus and hypothalamus. Neuroscience 66: 247-252.

Bialoskorska K, Taylor JRE, Djavadian R, Turlejski K (2001). Generation and apoptosis of the brain cells in the life cycle of shrews (Insectivora). Fifth International Congress of the Polish Neuroscience Society, Torun, Poland. Acta Neurobiol Exp (Wars) 61: 240.

Bizon JL and Gallagher M (2003) Production of new cells in the rat dentate gyrus over the lifespan: relation to cognitive decline. Eur J Neurosci 18: 215-219.

Benninghoff J, Schmitt A, Mössner R, Lesch K-P (2002) When cells become depressed: focus on neural stem cells in novel treatment strategies against depression. J Neural Transm 109: 947–962.

Bernstein L (1973) A study of some enriching variables in a free-environment of rats. J Psychosomatic Res 17: 85-88.

Betarbet R, Zigova T, Bakay RA, Luskin MB (1996) Dopaminergic and GABAergic interneurons of the olfactory bulb are derived from the neonatal subventricular zone. Int J Dev Neurosci 14: 921-930.

Bjarkam CR, Sorensen JC, Geneser FA (2003) Distribution and morphology of serotonin-immunoreactive axons in the hippocampal region of the New Zealand white rabbit. I. Area dentate and hippocampus. Hippocampus 13: 21-37.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000) Hippocampal volume reduction in major depression. Am J Psychiatry 157: 115-118.

Brezun JM, Daszuta A (1999) Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience 89: 999-1002.

Brezun JM, Daszuta A (2000) Serotonin may stimulate granule cell proliferation in the adult hippocampus, as observed in rats grafted with foetal raphe neurons. Eur J Neurosci 12: 391-396.

Cameron HA, Woolley CS, Gould E (1993) Adrenal steroid receptor immunoreactivity in cells born in the adult rat dentate gyrus. Brain Res 611: 342-346.

Cameron HA, McEwen BS, Gould E (1995) Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. J Neurosci 15: 4687-4692.

Chopin P, Briley M (1987) Animal model of anxiety: the effect of compounds that modify 5-HT neurotransmission. Trends Pharmacol 92: 881-894.

Claiborne BJ, Amaral DG, Cowan WM (1990) Quantitative, three-dimensional analysis of granule cell dendrites in the rat dentate gyrus. J Comp Neurol 302: 206-219.

Clemett DA, Punhani T, Duxon MS, Blackburn TP, Fone KC (2000) Immunohistochemical localization of the 5-HT_{2C} receptor protein in the rat CNS. Neuropharmacology 39: 123-132.

Corotto FS, Henegar JR, Maruniak JA (1994) Odor deprivation leads to reduced neurogenesis and reduced neuronal survival in the olfactory bulb of the adult mouse. Neuroscience 61: 739-744.

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E (2001) Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A 98: 12796-12801.

Czurko A, Hirase H, Csicsvari J, Buzsaki G (1999) Sustained activation of hippocampal pyramidal cells by 'space clamping' in a running wheel. Eur J Neurosci 11: 344-352.

Djavadian RL, Wielkopolska E, Bialoskorska K, Turlejski K (1999) Localization of the 5-HT_{1A} receptors in the brain of opossum Monodelphis domestica. Neuroreport 10: 3195-3200.

Duman RS, Nakagawa S, Malberg J (2001) Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology 25: 836-844.

El Mestikawy S, Taussig D, Gozlan H, Emerit MB, Ponchant M, Hamon M (1989) Chromatographic analyses of the serotonin 5-HT_{1A} receptor solubilized from the rat hippocampus. J Neurochem 53: 1555-1566.

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn A-M, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4: 1313-1317.

Feldberg W, Myers RD (1964) Effects on temperature of amines injected into the cerebral ventricles. A new concept of temperature regulation. J Physiol (Lond) 173: 226-231.

Freund TF, Antal M (1988) GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. Nature 336: 170-173.

Gage FH (2000) Mammalian neural stem cells. Science 287: 1433-1438.

Gheusi C, Cremer H, McLean H, Chazal G, Vincent JD, Lledo PM (2000) Importance of newly generated neurons in the adult olfactory bulb for odor discrimination. Proc Natl Acad Sci U S A 97: 1823-1828.

Globus A, Rosenzweig MR, Bennett EL, Diamond MC (1973) Effects of differential environments on dendritic spine counts. J Comp Phys Psych 84: 598-604.

Goldman SA, Nottebohm F (1983) Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain. Proc Natl Acad Sci U S A 80: 2390-2394.

Gould E, Gross CG (2002) Neurogenesis in adult mammals: some progress and problems. J Neurosci 22: 619-623.

Gould E, Cameron HA, Daniels DC, Woolley CS, McEwen BS (1992) Adrenal hormones suppress cell division in the adult rat dentate gyrus. J Neurosci 12: 3642-3650.

Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E (1998) Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A 95: 3168-3171.

Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ (1999a) Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 2: 260-265.

Gould E, Reeves AJ, Graziano MS, Gross CG (1999b) Neurogenesis in the neocortex of adult primates. Science 286: 548-552.

Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG (1999c) Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci U S A 96: 5263-5267.

Gratzner HG (1982) Monoclonal antibody to 5-bromo- and 5-iododeoxyuridine: a new reagent for detection of DNA replication. Science 218: 474-475.

Gross CG (2000) Neurogenesis in the adult brain: death of a dogma. Nature Rev Neurosci 1: 67-73.

Haddjeri N, Blier P, de Montigny C (1998) Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. J Neurosci 18: 10150-10156.

Haglund L, Swanson LW, Kohler C (1984) The projection of the supramammillary nucleus to the hippocampal formation: An immunohistochemical and anterograde transport

study with the lectin PHA-L in the rat. J Comp Neurol 229: 171-185.

Halasy K, Somogyi P. (1993) Subdivisions in the multiple GABAergic innervation of granule cells in the dentate gyrus of the rat hippocampus. Eur J Neurosci 5: 411-429.

Hamilton A (1901) The division of differentiated cells in the central nervous system of the white rat. J Comp Neurol 11: 297-320.

Haring JH (1991) Reorganization of the area dentata serotoninergic plexus after lesions of the median raphe nucleus. J Comp Neurol 306: 576-584.

Haring JH, Davis JN (1983) Topograhy of locus coeruleus neurons projecting to the area dentate. Exp Neurol 79: 785-800.

Haring JH, Davis JN (1985) Differential distribution of locus coeruleus projections to the hippocampal formation: Anatomical and biochemical evidence. Brain Res 325: 366-369.

His W (1904) Die Entwickelung des menschlichen Gehirns (Hirzel, Leipzig)

Jacobs BL (2002) Adult brain neurogenesis and depression. Brain Behav and Immun 16: 602–609.

Jacobs BL, Azmitia EC (1992) Structure and function of the brain serotonin system. Physiol Rev 72: 165-229. Jacobs BL, van Praag H, Gage FH (2000) Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 5: 262–269.

Jouvet M (1967) Neurophysiology of the states of sleep. Physiol Rev 47: 117-177.

Kaplan MS (1983) Proliferation of subependymal cells in the adult primate CNS: differential uptake of DNA labelled precursors. J Hirnforsch 24: 23-33.

Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. Nature 386: 493-495.

Kinsey AM, Wainwright A, Heavens R, Sirinathsinghji DJ, Oliver KR (2001) Distribution of 5-HT_{5A}, 5-HT_{5B}, 5-HT_6 and 5-HT_7 receptor mRNA in the rat brain. Mol Brain Res 88: 194-198.

Koprowska M, Krotewicz M, Romaniuk A, Strzelczuk M, Wieczorek M (2002) Fear behavior and regional brain monoamines distribution after R(+)-8-OHDPAT and R(+)-UH-301 injections into the dorsal raphe nucleus in rats. Acta Neurobiol Exp (Wars) 62: 63-74.

Kosofsky BE, Molliver ME (1987) The serotonergic innervation of cerebral cortex: different classes of axon terminals arise from dorsal and median raphe nuclei. Synapse 1: 153-168.

Kronenberg G, Reuter K, Steiner B, Brandt MD, Jessenberger S, Yamaguchi M, Kempermann G (2003) Subpopulations of proliferating cells of the adult hippocampus respond differently to physiologic neurogenic stimuli. J Comp Neurol 467: 455-463.

Krugers HJ, Koolhaas JM, Bohua B, Korf J (1993) A single stress experience alters glutamate receptor-binding in rat hippocampal CA3 area. Neurosci Lett 154: 73-77.

Kuhn HG, Dickinson-Anson H, Gage FH (1996) Neurogenesis in the dentate gyrus of the adult rat: age related decrease of neuronal progenitor proliferation. J Neurosci 16: 2027-2033.

Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, Schwartz GE (1997) Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia 35: 1437-1444.

Leger L, Charnay Y, Hof PR, Bouras C, Cespuglio R (2001) Anatomical distribution of serotonin-containing neurons and axons in the central nervous system of the cat. J Comp Neurol 433: 157-182.

Leibowitz SF, Shor-Posner G (1986) Brain serotonin and eating behavior. Appetite 7 (Suppl): 1-14.

Lemaire V, Aurousseau C, Le Moal M, Abrous DN (1999) Behavioral trait of reactivity to novelty is related to hippocampal neurogenesis. Eur J Neurosci 11: 4006-4014.

Lemaire V, Koehl M, Le Moal M, Abrous DN (2000) Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc Natl Acad Sci USA 97: 11032-11037.

Li XC, Jarvis ED, Alvarez-Borda B, Lim DA, Nottebohm F (2000) A relationship between behavior, neurotrophin expression, and new neuron survival. Proc Natl Acad Sci U S A 97: 8584-8589.

Lopez JF, Chalmers DT, Little KY, Watson SJ (1998) Regulation of serotonin$_{1A}$, glucorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. Biol Psychiatry 43: 547-573.

Lucki I (1992) 5-HT_1 receptors and behavior. Neurosci Biobehav Rev 16: 83-93.

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20: 9104-9110.

Merrill DA, Karim R, Darraq M, Chiba AA, Tuszynski MH (2003) Hippocampal cell genesis does not correlate with spatial learning ability in aged rats. J Comp Neurol 459: 201-207.

Miller MW, Nowakowski RS (1988) Use of bromodeoxyuridine-immunohistochemistry to examine the proliferation, migration and time of origin of cells in the central nervous system. Brain Res 457: 44-52.

Moghaddam B, Boliano ML, Stein-Behrens B, Sapolsky R (1994) Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. Brain Res 655: 251-254.

Moore RY, Halaris AE (1975) Hippocampal innervation by serotonin neurons of the midbrain raphe in the rat. J Comp Neurol 164: 171-184.

Nottebohm F (1985) Neuronal replacement in adulthood. Ann N Y Acad Sci 457: 143-161.

Nottebohm F (2002) Why are some neurons replaced in adult brain? J Neurosci 22: 624-628.

Parent A, Descarries L, Beaudet A (1981) Organization of ascending serotonin systems in the adult rat brain. A radioautographic study after intraventricular administration of [3H]5-hydroxytryptamine. Neuroscience 6: 115-138.

Phillips ML, Drevets WC, Rauch SL, Lane R (2003) Neurobiology of emotion perception I: The neural basis of normal emotion perception. Bio Psychiatry 54: 504-514.

Pinder RM, Wieringa JH (1993) Third generation antidepressants Med Res Rev 13: 259-325.

Radley JJ, Jacobs BL (2002) 5-HT_{1A} receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res 955: 264-267.

Ramon y Cajal S (1911) Histologie du System Nerveux de l'Homme et des Vertebres. Maloine, Paris.

Ramon y Cajal S (1913) Degeneration and Regeneration of the Nervous System (trans. R.M. Day from the 1913 Spanish ed.) Oxford University Press, London (1928).

Rakic P (2002) Adult neurogenesis in mammals: an identity crisis. J Neurosci 22: 614-618.

Rasmuson S, Olsson T, Henriksson BG, Kelly PA, Holmes MC, Seckl JR, Mohammed AH (1998) Environmental enrichment selectively increases 5-HT1A receptor mRNA expression and binding in the rat hippocampus. Mol Brain Res 53: 285-290.

Raymond JR, Mukhin YV, Gelasco A, Turner J, Collinsworth G, Gettys TW, Grewal JS, Garnovskaya MN (2001) Multiplicity of mechanisms of serotonin receptor signal transduction. Pharmacol Ther 92: 179-212.

Reynolds BA, Weiss S (1992) Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255: 1707-1710.

Ribak CE, Seress L, Amaral DG (1985) The development, ultrastructure and synaptic connections of the mossy cells of the dentate gyrus. J Neurocytol 14: 835-857.

Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, Lawton MT, McDermott MW, Parsa AT, Manuel-Garcia Verdugo J, Berger MS, Alvarez-Buylla A (2004) Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 427: 740-744.

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301: 805-809.

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psych 20: 11-21.

Seidenbecher T, Laxmi TR, Stork O, Pape HC (2003) Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science 301: 846-850.

Sheard MH (1969) The effect of pCPA on behavior in rats: relation to brain serotonin and 5-HIAA. Brain Res 15: 524-528.

Sheline YI, Sanghavi M, Mintun MA, Gado MH (1999) Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 19: 5034-5043.

Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E (2001) Neurogenesis in the adult is involved in the formation of trace memories. Nature 410: 372-375.

Sidman RL, Miale IL, Feder N (1959) Cell proliferation and migration in the primitive ependymal zone; an autoradiographic study of histogenesis in the nervous system. Exp Neurol 1: 322-333.

Siuciak JA, Boylan C, Fritsche M, Altar CA, Lindsay RM (1996) BDNF increases monoaminergic activity in rat brain following intracerebroventricular or intraparenchymal administration. Brain Res 710: 11-20

Skup M, Herrera DG, Ribeiro-da-Silva A, Cuello AC (1993) Neurogenesis in the rat hippocampus: lesion stimulated phenomenon? In: Neuronal cell death and repair (Ed. A.C. Cuello), Elsevier, Amsterdam, London, New York, Tokyo, p. 267-281.

Stanfield BB,Trice JE (1988) Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp Brain Res 72: 399-406.

Staubli U, Xu FB (1995) Effects of 5-HT3 receptor antagonism on hippocampal theta rhythm, memory and LTP induction in the freely moving rat. J Neurosci 15: 2445-2452.

Steward O (1976) Topographic organization of the projections from the entorhinal area to the hippocampal formation of the rat. J Comp Neurol 167: 285-314.

Sugita N (1918) Comparative studies on the growth of the cerebral cortex. J Comp Neurol 29: 61-117.

Suzuki WA, Clayton NS (2000) The hippocampus and memory: a comparative and ethological perspective. Curr Opin Neurobiol 10: 768-773.

Tanapat P, Hastings NB, Rydel TA, Galea LA, Gould E (2001) Exposure to fox odor inhibits cell proliferation in the hippocampus of adult rats via an adrenal hormone-dependent mechanism. J Comp Neurol 437: 496-504.

Tao Y, Black IB, DiCicco-Bloom E (1996) Neurogenesis in neonatal rat brain is regulated by peripheral injection of basic fibroblast growth factor (bFGF). J Comp Neurol 376: 653-663.

Tecott LH, Maricq AV, Julius D (1993) Nervous system distribution of the serotonin 5-HT_3 receptor mRNA. Proc Natl Acad Sci U S A 90: 1430-1444.

Thomas EA, Matli JR, Hu JL, Carson MJ, Sutcliffe JG (2000) Pertussis toxin treatment prevents 5-HT_{5A} receptor-mediated inhibition of cyclic AMP accumulation in rat C6 glioma cells. J Neurosci Res 61: 75-81.

Tork I (1985) Raphe nuclei and serotonin containg system. In: The rat nervous system (Ed. G. Paxinos). Academic Press, San Diego, London, p. 43-78.

Turlejski K (1996) Evolutionary ancient roles of serotonin: long-lasting regulation of activity and development. Acta Neurobiol Exp (Wars) 56: 619-636.

Van Praag H, Kempermann G, Gage FH (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 2: 266-270.

Van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH (2002) Functional neurogenesis in the adult hippocampus. Nature 415: 1030-1034.

Varrault A, Bockaert J, Waeber C (1992) Activation of 5-HT_{1A} receptors expressed in NIH-3T3 cells induces focus formation and potentiates EGF effect on DNA synthesis. Mol Biol Cell 3: 961-969.

Vertes RP, Fortin WJ, Crane AM (1999) Projections of the median raphe nucleus in the rat. J Comp Neurol 407: 555-582.

Vilaro MT, Cortes R, Gerald C, Branchek TA, Palacios JM, Mengod G (1996) Localization of 5-HT4 receptor mRNA in rat brain by in situ hybridization histochemistry. Mol Brain Res 43: 356-360.

Vollmayr B, Simonis C, Weber S, Gass P, Henn F (2003) Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. Biol Psychiatry 54: 1035-1040.

Whitaker-Azmitia PM (1991) Role of serotonin and other neurotransmitter receptors in brain development: basis for developmental pharmacology. Pharmacol Rev 43: 553-561.

Witter MP (1993) Organization of the entorhinal--hippocampal system: A review of current anatomical data. Hippocampus 3 (suppl.): 33-44.

Zhao M, Momma S, Delfani K, Carlen M, Cassidy RM, Johansson CB, Brismar H, Shupliakov O, Frisen J, Janson AM (2003) Evidence for neurogenesis in the adult mammalian substantia nigra. Proc Natl Acad Sci U S A 100: 7925-7930.

Received 22 March 2004, accepted 9 April 2004