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Neurogenic regions in the adult: relationship with the neuropsychiatric disorders

Gerardo Ramírez-Rodríguez,[1] María del Carmen Silva-Lucero,[1,2] Laura Gómez-Virgilio,[1,2] María del Ángel Ocaña-Fernández,[1] Leonardo Ortiz-López,[1] Mario O. Torres-Pérez,[1] Marco Antonio Meraz-Ríos[2]

Original article

SUMMARY

Neuropsychiatric diseases (NPD) are characterized for changes in the brain plasticity, which include neuronal loss in specific regions of the encephalon, changes in the synaptic transmission originated by alterations in the synaptic contacts and also by gene expression. Besides, another process which is a part of the brain plasticity and that is also affected in NPDs is the generation of new neurons (neurogenesis).

The neurogenic process in the adult is finely regulated by different factors such as genetic and cellular aspects, the microenvironment, as well as neurochemical, environmental and nutritional elements. Alterations of these factors impact the development and functioning of the new neurons.

Some trials run in humans have shown alterations in the neurogenesis in some NPDs. Nevertheless, the greatest advances have made use of animal models of NPD. In some cases the evidence has been controversial and it has recently been attempted to clarify using human pluripotent-induced stem cell cultures as models of NPD. Another model suggested for studying the alterations in neuronal development in NPDs are multipotent stem cells in the olfactory epithelium (MSCOE). However, evidence obtained with the MSCOE is scarce and it is necessary to prove whether a correlation with the alterations that occur in the neuronal development at a central level in the NPDs does or does not exist, or if MSCOE can show alterations observed in the NPDs where information about the factors that promote these diseases can be obtained.

Therefore, in this revision the basic aspects of neurogenesis and relevant information of the alteration of this process in the three neurogenic regions in the adult (hippocampus, olfactory bulb and olfactory epithelium) are included.

Key words: Neurogenesis, neuropsychiatric diseases, aging, stem cells.

RESUMEN

Las enfermedades neuropsiquiátricas (ENP) se caracterizan por cambios en la plasticidad cerebral que incluyen la pérdida neuronal en regiones específicas en el encéfalo, cambios en la transmisión sináptica originada por alteraciones en los contactos sinápticos y también por la expresión de genes. Además, otro proceso que forma parte de la plasticidad cerebral y que también se encuentra afectado en las ENP es la generación de nuevas neuronas (neurogénesis).

El proceso neurogénico en el adulto es regulado de manera fina por diversos factores como los aspectos genéticos, celulares, el microambiente, los elementos neuroquímicos, los ambientales y los nutricionales. Las alteraciones de estos factores impactan en el desarrollo y en la función de las nuevas neuronas.

Algunos estudios realizados en humanos han revelado las alteraciones en la neurogénesis en algunos ENP. Sin embargo los mayores avances logrados han utilizado modelos animales de ENP. En algunos casos estas evidencias son controvertidas y recientemente se han tratado de aclarar utilizando cultivos de células madre pluripotenciales-inducibles humanas como modelos de ENP. Otro modelo que se ha propuesto para estudiar las alteraciones en el desarrollo neuronal en las ENP son las células madre multipotenciales del epitelio olfatorio (CMPEO). Sin embargo las evidencias obtenidas con las CMPEO son escasas y resulta necesario demostrar si existe o no un correlato con las alteraciones que ocurren en el desarrollo neuronal a nivel central en las ENP, o bien si las CMPEO pueden mostrar las alteraciones observadas en las ENP que permitan obtener información acerca de los factores que promueven estas enfermedades.

Por lo tanto en esta revisión se incluyen aspectos básicos de la neurogénesis e información relevante de las alteraciones de este proceso en las tres regiones neurogénicas en el adulto: el hipocampo, el bulbo olfatorio y el epitelio olfatorio.

Palabras clave: Neurogénesis, enfermedades neuropsiquiátricas, envejecimiento, células madre.

[1] Laboratorio de Neurogénesis, Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz.
[2] Departamento de Biomedicina Molecular. Centro de Investigación de Estudios Avanzados (CINVESTAV). IPN.

Correspondence: Dr. Gerardo Ramírez-Rodríguez. Laboratorio de Neurogénesis. Division de Investigaciones Clínicas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz. Calz. México-Xochimilco 101, San Lorenzo Huipulco, Tlalpan, 14370 México, DF. Tel. 52 (55) 4160-5053. E-mail: gbernabe@imp.edu.mx

INTRODUCTION

The formation of new neurons obeys to a mechanism which is finely modulated and that responds both to intrinsic and extrinsic factors.[1,2]

Contrary to what was thought about the static nature of the adult brain, it is now known that the encephalon is capable of generating new neurons that can join the existent neural circuits to perform specialized functions like learning and memory, as well as permitting adaptation to new and complex circumstances.[3-6]

The first discoveries that indicated the formation of new neurons derive from the studies made by Joseph Altman in 1966, who reported the presence of cells with proliferative capacity in the adult brain. This project is one of the basis for the study of neuronal regeneration.[7]

Besides the hippocampus, another region of the brain where neuron generation takes place in a constitutive way is the olfactory bulb.[8,9] Both regions can be affected by the NPD.[10-14] Interestingly, some NPD also have alterations of the neural regeneration which takes place in the olfactory epithelium (OE), region of the nasal cavity in which, as in the hippocampus and the olfactory bulb, the neurogenic process occurs in a constitutive way.[15-21]

Neural regeneration of the three regions is due to the presence of multipotent cells which respond to different stimulus to carry out the formation of new neurons.[8,18,22-24]

NEUROGENESIS IN THE ADULT BRAIN: THE HIPPOCAMPUS

The hippocampus is a structure of the limbic system which takes part in memory processing and is one of the three regions where the generation of neurons takes place in a constitutive way.[4,5,7] In this structure, specifically in the dentate gyrus, new neurons derive from the stem cells that are located in the subgranular zone (SGZ)(Figure 1). Once the stem cells are divided, they give place to cells that amplify quickly. These cells migrate tangentially to start differentiating themselves into neurons, which will survive by developing dendrites that are projected towards the molecular layer[25] (Figure 1).

Since the hippocampus is a structure that is essential in the formation of the spatial memory[4,5] and also of memories related to emotions, it has been considered that hippocampal neurogenesis plays an important part in the formation and regulation of emotive and learning-related behaviors.[4,5] In this regard, and based on neuroanatomical, computational, electrophysiological, behavioral and imaging researches, a crucial part has been suggested for the new neurons of the hippocampus in the formation of episodic memory.[26]

NEUROGENESIS IN THE ADULT BRAIN: THE OLFACTORY BULB

The olfactory bulb maintains a five-layer fundamental organization: the olfactory nerve layer, the glomerular layer, the external plexiform layer, the mitral cell layer, and the granular cell layer. The non-myelinated axons of the bipolar sensory neurons, located in the olfactory epithelium, they fasciculate and penetrate the olfactory bulb in order to form the olfactory nerve layer. The terminals from these fibers form

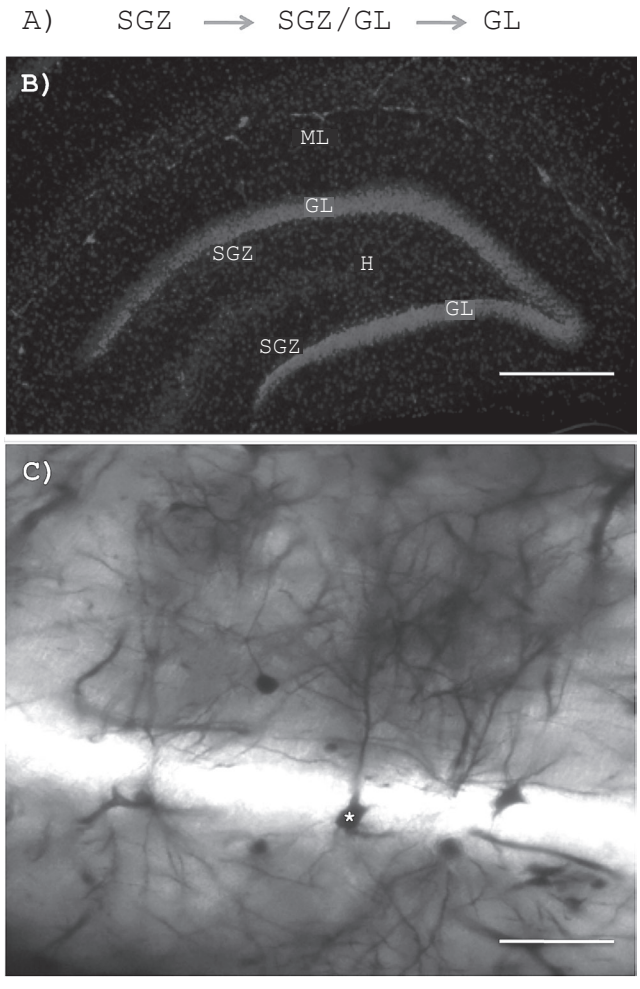

Figure 1. The neurogenic zone in the dentate gyrus. Panel A shows a sequence of the areas through which the stem cells and the neuronal precursors migrate until reaching the granular layer (GL), where new neurons are integrated in the hippocampus. The foregoing is clearly shown in panel B, in a micrograph of a coronal cut dyed with a nuclear marker. The micrograph shows the subgranular zone (SGZ), the molecular layer (ML) and the hilus zone of the dentate gyrus. The micrograph was taken with a fluorescence Nikon Eclipse Ti microscope. Panel C shows neurons of the GL of the dentate gyrus (DG) that were impregnated with metals using the Golgi-Cox technique. The asterisk indicates a granular cell with dendritic projections towards the ML. The micrograph was taken with a Leica DM500 clear field microscope. The calibration bar in B corresponds to 300 micrometers and in C to 60 micrometers.

synapses with the descending dendrites of the mitral cells in the glomerulus. The mitral cells are the primary efferent projection neurons of the olfactory bulb, and along with the tuft cells, they innervate the anterior olfactory nucleus and extend towards the olfactory tracts directly to the primary olfactory cortices[2] (Figure 2).

The new neurons of the olfactory bulb derive from the neuroblast which come from the stem cells which reside in the subventricular zone (SVZ), in the lateral ventricles[8,27] (Figure 2). The neurogenic process in the olfactory bulb starts with the splitting of stem cells to generate neuroblasts. These neural progenitors will migrate in groups through the rostral migratory stream until they reach the olfactory bulb, where terminal differentiation takes place. Once in the olfactory bulb, newly generated cells will form granular interneurons, as well as periglomerular neurons.[2] Thus, the newly generated interneurons replace the old granular cells to maintain the olfactory bulb circuitry fully functional.[28] This is interesting, since it points out that neurogenesis is important to the maintenance of the olfactory capacity and also for odor discrimination.[15] Considering the above, the olfactory bulb presents a very relevant part by processing the olfactory signals regarding its context, a signal that is transmitted to the olfactory bulb by the sensory neurons located in the olfactory epithelium[19,20] (Figure 2).

NEUROGENESIS IN THE OLFACTORY EPITHELIUM

The olfactory epithelium is analogous to the neural tube neuroepithelium, from which the brain in the embryo is developed.[29] This epithelium is located in the cribiform plate, the nasal *septum* and in the middle and upper portions of the turbinates.

Histologically, the olfactory epithelium is a heterogeneous tissue made out of olfactory bipolar and ciliar neurons, cells with microvilli, basal cells identified as the progenitors of the olfactory epithelium sensory cells, and sustentalcular cells.[15,30] Olfactory neurons present non-myelinated axons that form bundles, called olfactory fila, for crossing the foramen in the cribiform plate and are projected towards specific glomerular zones in the olfactory bulb.[15,17,30]

The olfatory epithelium is considered as a third neurogenic zone, external to the brain, since it presents the constitutive generation of sensory neurons, which is made by the neural progenitors residing in the epithelium.[17,18] Various works have shown molecular regulation and cell direction to carry out neurogenesis in the olfactory epithelium throughout the entire lifespan.[17,20,31] Continuous regeneration produced by the replacement of sensory neurons is regulated by the same growth factors or by neurochemical substances that promote brain development, both in the embryonic and the adult phase.[17,20,31]

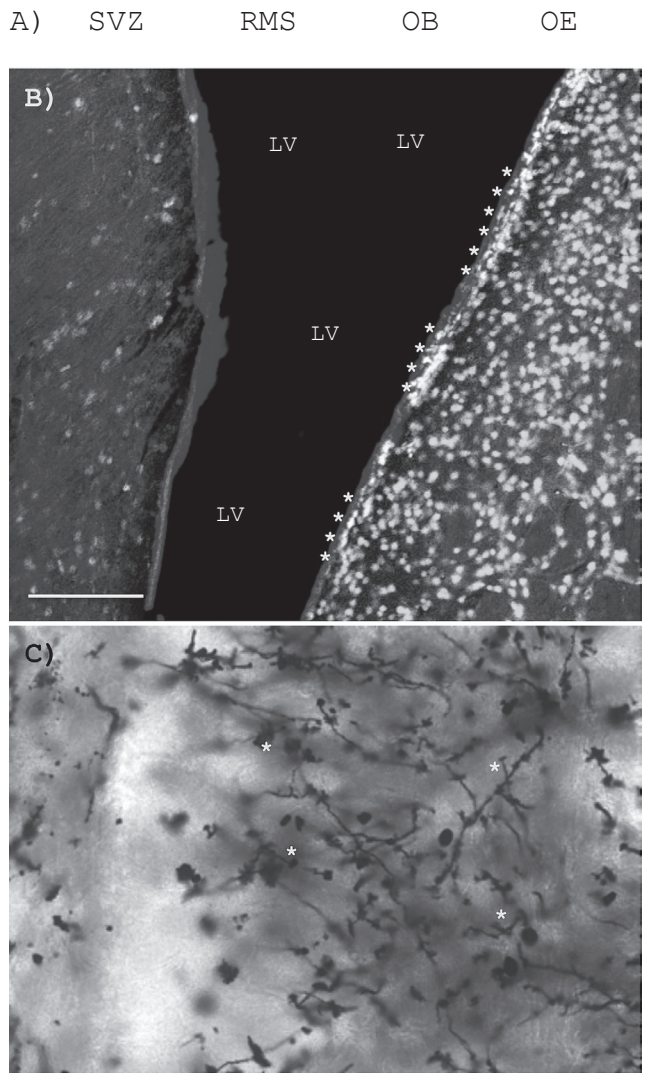

Figure 2. The neurogenic zone in the subventricular zone/olfactory bulb (SVZ/OB). Panel A shows the process for the generation of new neurons in the SVZ/OB. In addition, the rostral migratory stream (RMS) is included which helps neuroblasts migration until reaching the olfactory bulb (OB), the place where new neurons shall receive the projections coming from the sensorial neurons of the olfactory epithelium (OE). Panel B shows the lateral ventricles (LV) and cells under a proliferation status (asterisks). The micrograph was taken with a fluorescence Nikon Eclipse Ti microscope and the calibration bar is = 200 micrometers. Panel C shows neurons of the olfactory bulb (asterisks) that were impregnated with metals using the Golgi-Cox technique. Some cells show dendritic spines in their dendrites. The micrograph was taken with a Leica DM500 clear field microscope.

The olfactory epithelium cells, both in rodents and humans, present neural progenitors which express nestin protein, which belongs to the family of the intermediate filaments, supporting the cell structure; and also have a microtubule network made out of the neuron-specific protein called class III tubulin. Thus, those cells are responsible of the regeneration of the sensory neuron population of the olfactory epithelium through life and whose population is

in charge of transmitting the olfactory signals to the brain through the olfactory bulb[17,20,31] (Figure 2).

ALTERATIONS IN NEURONAL DEVELOPMENT IN THE ADULT AND IN NEUROPSYCHIATRIC DISEASES

Several studies made in various NPD have shown an interrelationship between them and the alterations in the neuronal development which takes place in the neurogenic zones.[10,11,13,31-35] Regarding this, we will now examine relevant information about the alterations of the neurogenic process caused by factors such as stress, and also about the alterations present in various neuropsychiatric diseases, such as Parkinson, Huntington, Alzheimer and schizophrenia. These neuropsychiatric diseases cause specific alterations in the neurogenic process in the hippocampal dentate gyrus, the olfactory bulb while some of them are also present in the olfactory epithelium.

Stress

The hippocampus is a structure of the limbic system which is altered in its structure, as well as in its function, in patients with neuropsychiatric disorders.[6] Alteration in the hippocampus has also been observed in preclinical trials, in which animal models of neuropsychiatric diseases have been used.[6] Among the affected processes hippocampal neurogenesis may also be included.[6]

Regarding this, stress is an important factor for the presence of anxiety and for the development of major depression. Preclinical trials show that neurogenic process is affected by exposure to stressors. Interestingly, acute stressors mainly affect the proliferation of progenitor cells in the hippocampus DG, without affecting differentiation and survival. On the other side, chronic stress affects cell proliferation as well as cell differentiation and survival. Research done in humans has also revealed that the effects of stress in the neurogenic process are reverted by antidepressants, this being the first report that indicates that cell proliferation decrease in the human brain can be reverted. This supports a hypothesis that says that in alterations of the brain plasticity present in depression and anxiety, hippocampal neurogenesis is one of the factors that can be affected.[32,36-42] Lately, this information has been widely revised.[43]

Schizophrenia

This is a neuropsychiatrical disease that presents alterations in the early neuronal development.[44-48] It is a multifactorial NPD and it has been said that between the factors which converge for it to be developed, we have genes and the environment, as well as neurochemical and brain related structural differences, such as changes in the neuronal plasticity.[31,45,46,49,50]

The first symptoms, such as hallucinations and deliriums, become evident during puberty and early adulthood (between the age of 16 and 30); however, in some cases the disease appears at the age of 45.[45] Diagnosis or identification of the progressive changes is important because with therapeutic intervention, in theory, many of the symptoms can be eased.[45]

Interestingly, it has been proven that, at a cellular level, there are not any changes in the proportion of cells; however, these are more densely packed due to a relative dystrophy of its dendritic arborizations and to changes in the neuropil.[47] This suggests that the changes in brain structure are part of the development of schizophrenia. Considering neurogenesis is included in neural plasticity, it is therefore viable to think that the de *novo* production of neurons, oligodendrocytes and astrocytes is adequate; on the other hand, the insertion of new neural elements to the existing networks can be altered, in conjunction with the presence of synaptic pruning, mielinization and abnormal presence of apoptosis.[50]

Among the factors on a genetic level, it has been considered that the haploinsufficiency of the gene which codifies for the protein disrupted in schizophrenia-1 (DISC1) is one of the risk factors for schizophrenia that have better been established.[51] The repression of DISC1 signaling leads to an accelerated dendritic development in the newly generated neural cells, as well as an increment in migration, which causes an inadequate integration of these new cells to the neural network.[52]

Alterations in the neuroplasticity present in schizophrenia can also be caused by signaling cascades in some growth factors. Clinical evidence shows that the pathway of the transforming growth factor (TGF-β) is hyperactive, while the *Wnt* pathway is hypoactive. Results obtained from the analysis of the cell signaling pathways show an accelerated differentiation and migration, which affects the proper insertion of new neurons.[50] Another signaling pathway implicated in the pathophysiology of schizophrenia is the retinoid,[53,54] which plays a central role in the early neurodevelopment processes like neurogenesis.[54,55] A rise in the expression of one retinoid receptor in the granular cells of the hippocampus has been recently described.[55] The aforementioned receptor works as a switch to control the transition of proliferation events unlike those of stem cells during development.

Increased expression of this receptor in the granular cells of the dentate gyrus during schizophrenia can be a consequence of defective early development or altered neurogenic processes in the adult brain.[56]

Patients with schizophrenia also present an increase in the cavity of the lateral ventricles, where the stem cells which will form new neurons in the olfactory bulb are

found[56,57] (Figure 2).This could be affecting the formation of neurons in the olfactory bulb and, somehow, neurogenesis in the olfactory epithelium could also be altered.[56]

Regarding this, in explants of the olfactory epithelium from patients with schizophrenia, a rise in proliferation and cellular death rates has been found. Thus, altered cellular proliferation in the olfactory epithelium concurs with the changes in both neural precursors and olfactory neurons of individuals with schizophrenia. These results suggest a dysregulation in the olfactory neurogenesis.[58]

Apart from DISC-1, also the expression of the transcripts of RAD51L1, NCK2 and VIPR1 are increased in schizophrenia.[29] The expression levels of proteins codified by the genes NCK2 and VIPR1 are directly related with altered cellular proliferation in the cells of the olfactory epithelium; while RAD51L1 phosphorylates cyclin E, cdk2 and p53 and thus affects the phase G1 synchronization of the cell cycle. Contrariwise, it has been seen that the expression of two genes involved in neurogenesis (PTN, NTF5) and another gene involved in neural differentiation (NPDC1) is diminished in the olfactory epithelium cells. The reduced expression of genes concerned in the neural differentiation is also consistent with the observation of an increase in the cellular proliferation caused because, for example, NDPC1 is expressed only in neural cells when they stop their division and start differentiating themselves.[29] Altogether, it has been shown that alterations in the neurogenic process exist in schizophrenia, both in the hippocampus and in the olfactory bulb and epithelium.

Parkinson's disease

It is a disorder of the motor system common in elderly people, characterized by trembling, stiffness, among other symptoms that will interfere with the daily activities of the patients. In PD dopaminergic neurons of the substantia *nigra pars compacta*, which is a basal ganglion of the midbrain, are degenerated selectively. These neurons are projected towards the GABAergic neurons in the striatum and participate in the coordinate muscular movements. In addition, cholinergic cells in the basal nucleus, the serotonergic system in the *raphé* nucleus, the amygdale, the hippocampus, the olfactory bulb, and the temporal and cingulate cortices show cell degeneration.[13,59] PD does not seem to be associated with a hereditary genetic mutation, however, various genes have been suggested as factors for its development. The mechanism leading to neural death has not been clarified either.[13,59-61]

In the etiology of PD, participation of environmental factors such as lifestyle, toxins, and aging, as well as some genetic factors, has been suggested. Trials made in animal models based on neurotoxin induced damage have shown alterations in the neurogenic process, specifically in proliferation and cell survival events.[59,62]

Interestingly, significant decrease in cellular proliferation in the SVZ in patients with PD, as well as in animal models with the same disease has been seen.[59] In PD models with neurotoxins, increase in the amount of dopaminergic interneurons in the glomerular layer of the olfactory bulb can be seen. Similarly, trials in patients with PD show an increase in dopaminergic neurons.[13,62]

Considering the above, it is necessary to conduct preclinical trials that show the degree of affectation, not only in the substantia *nigra*, but also the possible changes in neural regeneration present in the olfactory epithelium, since alterations in the olfactory capacity of patients with PD have also been described.[63] In this regard, precursor cells of patients with PD have been recently isolated, a model with which alterations present in neurogenesis in the olfactory epithelium are intended to be addressed, and also to obtain information about the genetic complexity and the environmental interactions which contribute to the development of various neuropsychiatric diseases.[64] Even though this and various other cellular models have been suggested (Figure 3), it is necessary to establish whether isolated cells display the capacity to show changes located at a central level in all neuropsychiatric diseases, or only in the ones that have alterations or loss of the olfactory capacity.

Huntington's disease

This is an autosomal dominant inheritance disease with progressive symptoms that include involuntary movements, cognitive impairments and psychiatric disturbances. The most remarkable pathophysiology of the disease is the progressive degeneration of the neuron progression and an increased gliosis, leading to striatum atrophy, adjacent to the sub-ventricular zone. HD is caused by a CAG repeat expansion in the code gene for the huntingtin protein.[25] This protein is cytoplasmic and it is associated with the microtubules and vesicles. The protein participates in organelles traffic.[65,66] It has been recently reported that the huntingtin-1 is responsible for the generation of growth factors gradient, nutrients and neurotransmitters, promoting the cerebrospinal fluid homeostasis.[65,66]
The *post-mortem* brain analysis of HD patients shows that the sub-ventricular zone becomes thicker, with an increase of the cellular proliferation, meanwhile transitory amplification cells and neuroblasts moderately increase in number.[67] This neurogenesis alteration has been described in the HD transgenic mouse model, the R6/2 mice, which carry the human HD genes with enlarged CAG repeat.[68]

In R6/2 rodents an increase in the self-renewal capability of the ZSV stem cells population has been noticed, which occurs in parallel with the disease progress. Also, the neuroblasts and the new generation neurons migrate to the striatum of these mice. In addition, the neuroblasts migration to the olfactory bulb is inhibited significantly. This is interesting because of its impact in the generation

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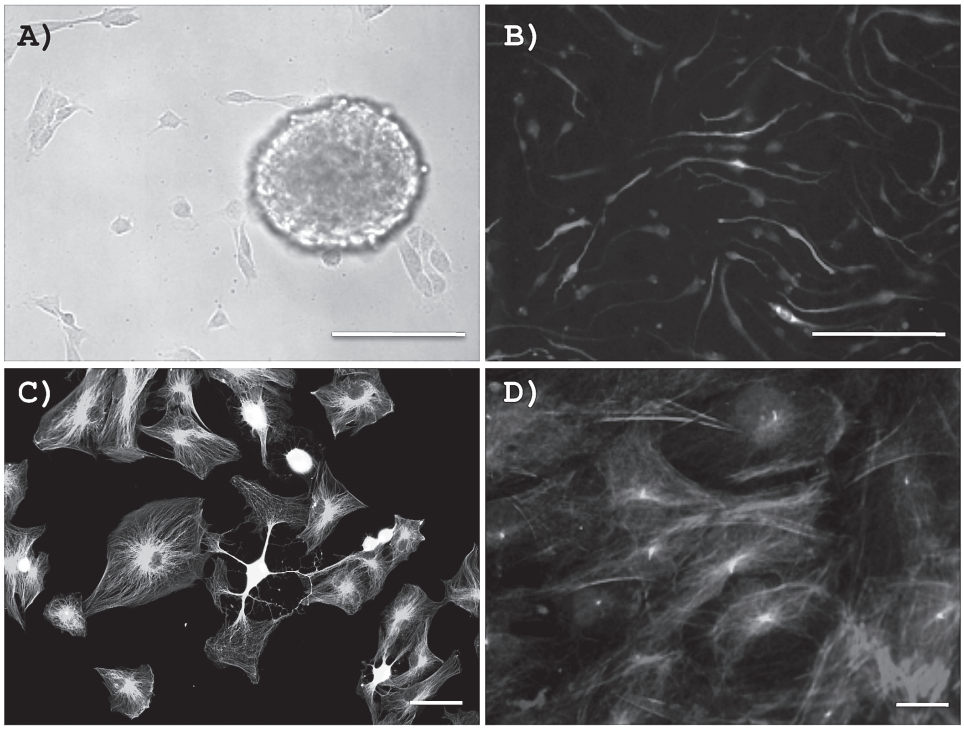

Figure 3. The stem cells and the precursors of the three neurogenic zones. Panel A shows a clump of cells making up a neurosphere due to the proliferative capacity. Panel B shows cells differentiated from the stem cells located in the subgranular zone of the dentate gyrus of the hippocampus. Panel C shows isolated cells from the lateral ventricles that give rise to the olfactory bulb neurons. Panel D shows isolated stem cells of the olfactory epithelium. The calibration bar in panels A and B = 80 micrometers; while C = 30 micrometers and D = 15 micrometers. All images were taken with a fluorescence Nikon Eclipse Ti microscope.

of new neurons which must be located in the olfactory bulb, in such a way that the odor discrimination by the HD patients and also by the animal model (R6/1 rodents) is disturbed, probably due to the diminution in the neuron replacement in this structure.[69] All this can be also affected by an erroneous assembly of the cilium, since it has been demonstrated that the deletion of the gene that codifies for huntingtin in the ZSV ependymal cells alters the primary cilium formation, therefore affecting negatively the neuroblast migration.[65,66]

Similarly, and taking into account the alterations in odor discrimination and the decrease in the generation of new neurons in the olfactory bulb, it can be said that the sensory neuron formation in the olfactory epithelium is also altered; in such a way that the whole system which is involved in olfaction (olfactory epithelium-olfactory bulb)would remain damaged in HD.

Alzheimer's disease

This neuropsychiatric disease presents progressive neuronal degeneration characterized by gradual diminution both of memory and of the execution of higher cortical functions. It is the most common type of dementia and it represents approximately 60 to 70% of all cases. The neuropathologic characteristics of the disease include atrophy, neuronal loss, neurofibrillary tangle formation and senile plaques.[13,33,35,62,70]

In 1907, Aloïs Alzheimer described the case of a 51-year-old patient presenting a dementia case with severe disorientation and hallucinations. The microscopic study of this woman's brain allowed for the discovery of the existence of injuries in the form of insoluble aggregates, which that author named neurofibrillary degeneration, which coexisted with neuritic plaques. The discovery of the clinical record of this patient has allowed for the progress and development of the study of the disease.[13,31,33,62]

Recent studies made in humans with the AD showed an increase in neurogenesis.[70] In this case, the expression of protein markers of immature neurons was measured that suggest the formation of new neurons in the hippocampus of AD patients. In relation with the controls, brains with Alzheimer's disease showed an increment in the expression of the DCX and TUC-4 in the SGZ of the DG of the hippocampus. Another study showed that in the pre-senile variety there is a further proliferation in the CAI-3 layers, maybe reflecting the glial and associated vascular changes, but not neurogenesis.[32] In contrast with the results obtained in *post-mortem* human tissue, adult neurogenesis is de-

creased in the Alzheimer's disease transgenic mouse model (TgCRND8 mice), which overexpress the human amyloid precursor protein (APP).[71]

The extracellular accumulation of the β–amyloid peptide is an important event in the DA pathogenesis. Most of the studies have been focused in mechanisms where the peptide induces the adult neuron degeneration in such a manner that the intracerebroventricular infusion of the peptide causes damage in the ZSV neurogenesis of the adult mouse. Besides, it has been demonstrated that the presence of oligomeric forms of the Aβ peptide, either $A\beta_{1-40}$ and/or $A\beta_{1-42}$, produced as a consequence of the amyloidigenic processing of the amyloid precursor protein (APP), has an effect in the neurogenesis of both regions of the brain, the SGZ of the DG and in the ZSV of the walls of the third ventricle. All of the above occurs long before the formation of the amyloid plaques as well as of neurofibrillary tangles and neuronal loss, all of which are characteristics of the disease.

In relation to the olfactory dysfunction, the olfaction abnormalities in AD include diminution in the odor detection threshold, clear deficits in the odor recognition ability and damages in the odor memory recognition. In a meta-analysis of studies for odor detection threshold, olfactory identification and recognition memory, deficits were found in the three domains in AD. This may indicate participation both of the "peripheral" olfactory structures (for example, the olfactory neuroephitelium) responsible for odor detection, as well as the "central" olfactory regions of the brain (for example, the olfactory bulb, the anterior olfactory nucleus, the prepyriform cortex, the amygdala, the entorhinal cortex, the basal prosencephalon) responsible for the odor identification and olfactory memory.[31,33,35] Several studies have examined cellular loss and its degeneration, neurofibrillary tangles and senile plaques in the olfactory bulb of patients with AD. The neurofibrillary tangles are present in the anterior olfactory nucleus and only in a few cases mitral cells, tuft cells, and external granular cells are also present. Just as well, degeneration and loss of mitral cells has been reported in the anterior olfactory nucleus. In addition to the above, senile plaques have also been observed in this olfactory nucleus[31] in such way that the amount of neurons in the anterior olfactory nucleus has been substantially reduced in AD patients, as compared with the controls.[33]

In relation with the neurogenic zone located in the olfactory epithelium, in 1989 a presence of a new neuritic pathology form was described in AD patients, as well as a diminution in the amount of sensory olfactory neurons. Subsequent studies were carried out to determine the presence of characteristic AD neuropathologies like neurofibrillary tangles and senile plaques. Attempts were also made to discover if the expression of particular epitopes of the *tau* protein allowed distinguishing different stages of the disease. While neurofibrillary tangles were not observed in the OE of some of the cases studied, *tau* immunoreactivity was evident in dystrophic neurites.[31,33]

In contrast with previous studies, when a nasal mucosa biopsy from AD patients was obtained, immunoreactivity to *tau* protein was described in the dendrites and in the olfactory neurons soma, in such way that extracellular plaque deposits immunoreactive to *tau* were observed, as well as immunoreactivity to dendritic ubiquitin. Abnormal findings were most common in AD cases but were also present in control cases. The olfactory dysfunction observed in AD patients is directly related to the presence of intracellular and vesicular amorphous aggregates of peptide Aβ as well as expression of hyperphosphorylated *tau* with a typical AD appearance, such as neurofibrillary tangles, both of them in the olfactory epithelium. On the other hand, the olfactory neurons in Alzheimer's patients also develop pathology associated to the disease, including neuronal loss, a great amount of neurofibrillary tangles and amyloid plaques. The cultures of these neurons have shown elements of the cerebral pathophysiology of AD, as well as abnormal processing of the amyloid precursor protein.[13,31,33]

Since there is an abnormal processing of amyloid protein in the neurons from the olfactory epithelium, analogous to what happens in the brain and which equally develops the disease related pathology, it is feasible to assume that the presence of oligomeric forms of Aβ in the olfactory epithelium neuronal cells, which have regeneration capability, may have an effect on its neurogenic potential and somehow directly affect the olfactory dysfunction observed in AD patients.

Epilepsy

Apart from the neuropsychiatric disorders mentioned above, epilepsy, a neurologic disorder, also has strong links with the function and structures of the hippocampus, in particular with its neurogenesis.[72] For instance, intense seizure activity increases SGZ cell proliferation, which causes the formation of a greater number of neurons.[72]

These results are particularly interesting because neonatal seizures seem to be related with long term defects upon sensibility to seizures, cognition and hippocampal volume.[73]

In addition to the above, it has also been reported that the short seizure activity as well as the long one reduce the number of new generation granular cells, when analyzed at postnatal day 17 and a week after the seizure occurs. These results helped in understanding how the neonatal seizures affect neuronal development and neural circuit formation.[74] This work adds up to a growing appreciation of the fact that neurogenic response to seizure activity depends on age, a fact relevant for understanding the increased incidence in the occurrence of seizures whether in childhood or late adulthood. For example, meanwhile experimentally induced activity in adulthood increases the SGZ proliferation, seizure activity in old age is not associated with its

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increase.[75] Seizures can also produce aberrant morphology and migration in new neurons accompanied with alteration in the synaptic function,[76] hence aberrant neurogenesis is probably one of many hippocampus abnormalities that contribute to epilepsy and/or cognitive dysfunction.

CONCLUSIONS

In this work we review relevant information which supports the presence of neuron generation in a constitutive way in three neurogenic zones during adulthood: the hippocampus, the olfactory bulb and the olfactory epithelium.

Altogether, all evidence hereby mentioned shows that alterations in the neurogenic process are relevant, although not in an exclusive way, in causing the development of neuropsychiatric and neurological diseases. Interestingly, in some of these diseases, such as Huntington's and Alzheimer's disease, as well as schizophrenia, changes in the neurogenic process are presented in the three zones, which gives us information about the alterations occurred in the systems involved in memory and smell perception, event in which the formation of memory is also a part. This can explain alterations and deficits in both functions in various neuropsychiatric diseases.

It is important to remark that changes in the neuronal development present in neuropsychiatric diseases have been made clear in animal models and, in some cases, in human *post-mortem* tissue. Even though, to this date, there is not a full panorama due to the multifactor nature of these ailments. In an attempt to generate more information about alterations in neuronal development, present in these neuropsychiatric diseases, cellular models derived from patients with a specific disease have been used. These models reflect changes of the neurogenic region from which cells are isolated, without showing, to date, changes that occur in other regions, and have only shown correlation with the presence of a neuropsychiatric disease. This is understandable; especially because each neurogenic region develops neurons specialized for a specific function.

Finally, we consider that studying the neurogenic process is important because it is one of the factors which are altered in neuropsychiatric diseases, and due to the specialized function of each neuronal type formed in the neurogenic zones of the adult, information about changes in the neuronal development in each neurogenic zone and its possible relation to a disease can be obtained. Some studies developed by our group are headed towards knowing and understanding the cellular biology of the neural origin stem cells present in adulthood, for future application (Figure 3). We expect to understand the impact of the alterations in the neurogenic process for the development of various neuropsychiatric diseases and/or the benefit of neurogenesis stimulation to delay the effects of aging on the neural plasticity.

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