Alzheimer’s disease (AD) is a neurodegenerative illness and is the most common form of dementia. This pathology causes behavioural issues, disorientation, mood swings and cognition worsening. Some of them had been noticed in artwork (see Figure 1).

This disease is spread in worldwide and the all cases of dementia, AD represents 70%. The molecular mechanism of AD is explained by amyloid cascade hypothesis, which is the most influential model of pathology (Figure 2). This theory proposes that in AD patients takes place amyloidogenic pathway whereas the non-AD patients carry out non-amyloidogenic pathway.

The amyloid precursor peptide (APP) is a transmembran protein. APP can be processed by three enzymes: α-, β- and γ-secretase. If APP is processed by a secretase, the precursor will generate a soluble molecule named sAPPα and takes places non-amyloidogenic pathway. Nevertheless, the cleavage due to β- and γ-secretase leads to amyloidogenic pathway. The β-secretase splits APP and it’s formed a soluble molecule sAPPβ, and the performance of γ-secretase releases fragments of β-amylod peptides (Aβ), a basic species.

The senile plaques are formed by the accumulation of Aβ in extracellular space. These deposits can be internalised by cells leading to cell death.

The amyloidogenic pathway is the neurofibrillary tangles reduce neurogenesis in this neurogenic niche and granular cells in dentate gyrus. The depletion of these cellular (Figure 11A). Moreover, the production of new neurons in dentate gyrus normal manner because cytoarchitectonics are normal at early ages migration and settling of granular neurons in dentate gyrus occurs in a normal manner (Figure 11B). The new neurons, which arrive at olfactory bulb, can be mature or young neurons. These cells migrate to catch up the granular or periglomerular layer to integrate in neural network.

In the adult mammalian CNS, there are two know “neurogenic niche”, the subventricular zone (SVZ) of lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus.

Subventricular zone

Embryonic radial glia gives rise type B cells (astrocyte) which have the capacity of self-renewing and originate type C cells (transit progenitor); see Figure 5. These cells give rise neuroblasts (type A cells) which migrate to olfactory bulb through rostral migratory stream (RMS) (Figure 6). The new neurons migrate from lateral ventricle (SVZ) to affecting bulb (OB) through rostral migratory stream (RMS). Subventricular zone of dentate gyrus (SGZ) is also indicated (Figure 7).

While the neural precursor cells are differentiating, these are moving within dentate gyrus radial or transversally. These precursor give rise neuroblasts which migrate along dentate gyrus generating glutamatergic granule cells. These granule cells make grow up arbor to CA-3 and ramifying dendrites to molecular layer of dentate gyrus.

The information flows from glutamatergic granule cells to CA-3, the CA-3 neurons receives the information and it’s send to CA-1. From this field, the information is send to deep layers of entorhinal cortex. Finally, the information come back to glutamatergic granule cells of dentate gyrus (Figure 10).

In AD, amyloid plaques are found in the cortex volume and the presence of senile plaques (Figure 3B). The people with AD show lesions in temporal cortex (Figure 11A), and the neurodegeneration is associated with the temporal cortex. The cell’s loss is occurring in stages, the first stage is the cell’s death (Figure 11B). The second stage is the cell’s disappearance (Figure 11C) and third stage is the cell’s replacement (Figure 11D).

ADULT NEUROGENESIS AND ALZHEIMER’S DISEASE: WHAT CAN WE LEARN?

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Introduction

Adult neurogenesis under normal conditions

In adult mammals, the CNS contains two neurogenic niches, the subventricular zone (SVZ) of lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus. In these zones, progenitor cells divide leading to the production of new progenitors (1). These progenitors give rise to neuroblasts which migrate along the dentate gyrus generating glutamatergic granule cells. These granule cells grow up arbor to CA-3 and ramifying dendrites to molecular layer of the dentate gyrus. The information flows from glutamatergic granule cells to CA-3, the CA-3 neurons receive the information and send it to CA-1. From this field, the information is sent to deep layers of entorhinal cortex. Finally, the information came back to glutamatergic granule cells of dentate gyrus (Figure 10).

Materials and methods

3xTg-AD mouse model harbours human mutations:

- APPsw
- PS1M146L
- TauP301L

3xTg-AD females show amyloid and tau-pathologies homologous to humans. Mice present severe depletion of neurons in several areas of the CNS including central cortex, amygdala and hippocampus.

Aims

1. To study how neurogenesis takes place in adult brains.
2. To understand how Alzheimer’s disease alters adult neurogenesis in 3xTg-AD mice, a murine model of this neurodegenerative entity.
3. To extrapolate the affects in 3xTg-AD mouse model to humans patients affected with Alzheimer’s disease.

Subgranular zone

During early development of the dentate gyrus, granule cells are originate from cellular precursors located in the neuromechanism. Some of them persist in the adult dentate gyrus and establish a secondary neurogenic region in the subgranular zone. This is composed by type 1 cells, which are neural stem cells localised on spanning of granule cell layer and ramifying in inner molecular layer of dentate gyrus (Figure 7).

Type 1 cells give rise amounts of type 2 cells, a neural precursor cell (NPC), according to specific markers expression (see Figure 8 and 9).

Figure 6. Formation of granule cells in the adult dentate gyrus (1)

While the neural precursor cells are differentiating, these are moving within dentate gyrus radial or transversally. These precursor give rise neuroblasts which migrate along dentate gyrus generating glutamatergic granule cells. These granule cells make grow up arbor to CA-3 and ramifying dendrites to molecular layer of dentate gyrus.

The information flows from glutamatergic granule cells to CA-3, the CA-3 neurons receives the information and it’s send to CA-1. From this field, the information is send to deep layers of entorhinal cortex. Finally, the information come back to glutamatergic granule cells of dentate gyrus (Figure 10).

Results

Subsequent zone is the place where the hippocampal stem cells (NPC) renew and originate neurons (Figure 9).

Literature data from female 3xTg-AD indicate:

- Before the symptoms of Alzheimer’s disease appears, the generation and settling of granular neurons in dentate gyrus occurs in a normal manner because cytoarchitectonics are normal at early ages (Figure 11A). Moreover, the production of new neurons in dentate gyrus and the number of cells are conserved.
- In mature 3xTg-AD mice, there is affectation in stem cells and its progeny, and granular cells in dentate gyrus. The depletion of these cellular populations is progressive with age of mice, and the senile plaques and neurofibrillary tangles reduce neurogenesis in this neurogenic niche (Figure 13B).
- Regeneration is disturbed in 3xTg-AD due to the massive loss of stem cells and its progeny leading to an imbalance impossible to restore. I propose that a similar scenario occurs in patients affected with Alzheimer’s disease (Figure 11C).

The disease’s study in triple transgenic mouse model allows to extrapolate the results to humans (Figure 12):

1. AD patients contain equal cytoarchitectonics and the same number of cells in dentate gyrus in comparison with healthy people.
2. This neurodegenerative entity affects neural stem cells and its progeny in subgranular zone of dentate gyrus.
3. The regeneration is disturbed by the disease leading to an imbalance impossible to restore.

Conclusion

This neurological entity is characterized by reduction of cortex volume and the presence of senile plaques (Figure 5A) and neurofibrillary tangles (Figure 3B). The people who suffer this illness shows impairments in memory because the first field affected is the hippocampus.

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