IMPACT OF ACUTE TRAUMATIC BRAIN INJURY ON THE SENSE OF SMELL: THE ROLE OF SMELL TRAINING AND NEUROPROTECTION IN POST-TRAUMA SMELL RECOVERY

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1. Abstract

1.1. Principal goals

1. To determine the presence of partial (hyposmia) or total (anosmia) loss of smell in patients who have suffered acute traumatic brain injury (TBI), as well as the possible recovery of the sense of smell after smell training.

2. To investigate the olfactory dysfunction and the molecular changes induced by a partial or total excitotoxic lesion of the olfactory bulbs, as well as possible smell and neuronal recovery through training and with neuroprotector treatment, in an animal model of secondary neuronal degeneration in TBI.

1.2. Principal findings

A) In patients who have suffered a TBI because of traffic, workplace or domestic accidents:

1. The loss of smell is much more frequent (4 out of 10 persons) with predominance (70%) of total loss of smell or anosmia.

2. The loss of smell (in detection, memory and identification of smell) correlates with the brain damage observed by magnetic resonance in the smell structures (smell tracts and bulbs) and is clearly associated with food disorders (3.5 times more) and behavioural changes (5 times more).

3. Smell training through the BASTAT-6 smell battery could be considered as a type of beneficial therapy in improving the perception of smells although this recovery is slight, linked to continual training and especially in patients with partial olfactory dysfunction or hyposmia.

B) In the animal model of excitotoxicity in rat induced by bilateral administration of the neurotransmitter N-methyl-D-aspartate (NMDA) in the olfactory bulbs (OB):

1. The lesioned animals presented an olfactory dysfunction and a restructuring of the cellular layers of the OB associated to a decreased volume of the OB (by magnetic

resonance) and to alterations in neurogenesis in the subventricular zone and to changes in the cell populations of the OB (by flow cytometry).

2. The smell training induces the recovery of the smell function in the lesioned animals.

3. The treatment at low doses of MK801, antagonist of the NMDA receptors, has a beneficial (neuroprotector) effect, improving the olfactory dysfunctions.

4. Cellular cultures of OB were obtained in which we were able to characterise the three cell populations: neurones, glial cells and proliferative cells. In the three cell populations, the administration of NMDA induced cellular death. These findings make it possible to open up a new line of research in new neuroprotective treatments with the aim of attenuating olfactory dysfunction in patients with TBI.

1.3. Relevance and practical application:

1. The preparation of a score for brain damage by image (MR) as an indicator of the lesion of smell structures in patients with TBI and correlation with the seriousness of the olfactory dysfunction.

2. The marketing and possible patenting of a battery of 6 odorants (BASTAT-6) to facilitate smell rehabilitation in patients with TBI and loss of smell.

3. The creation of these animal and in vitro models of secondary neuronal degeneration in TBI will be useful both for studying the physiopathology and mechanisms of excitotoxicity that occur early on in this pathology and for the investigation of new treatments with neuroprotective drugs.

4. The consolidation of a multidisciplinary collaboration (rehabilitators, radiologists, neurologists and ENT specialists) in the management of patients with TBI and loss of smell.

2. Results

I. CLINICAL STUDY of patients with TBI (Institut Guttmann, Hospital Clínic):

1. More than a third of the patients (37.5%) who have suffered acute traumatic brain injury (TBI) due to an accident (traffic, work or domestic) have loss of smell, with a predominance of total affectation (70%) over partial (30%).

2. We observed no neurocognitive differences between the two groups of cohort A (with or without smell loss), although the score for independence (measured by the FIM test) was greater in the patients with loss of smell. This correlates with the seriousness of the TBI, and it was observed that the loss of smell was manifested with greater frequency in the patients with less serious TBI of ($p<0.05$).

3. Most of the patients with TBI and loss of smell presented frontal encephalomalacia (73%), unilateral or bilateral bulbar neuromalacia (67.6%) and chronic bulbar haemorrhage (51.4%). The score for the cerebral affectation by MR related to the smell pathways (4.9±0.3) was slight, with a greater affectation in the left side. High variability was observed in the volume of the olfactory bulbs, making it difficult to correlate with the olfactory dysfunction of each individual patient. The mean bilateral bulbar volume in the patients with TBI and loss of smell was less (106 mm^3) than in the population without TBI (120 mm^3), but with no significant differences between right and left.

4. In the patients of the smell training group, but not in those of the control group without training, an improved sense of smell was observed, both by EVA and by BAST-24 (forced identification), after 3 months of training, and with a tendency to be lost on cessation of smell training.

FINAL CONSIDERATION. The loss of smell is manifested much more frequently (1 out of 3) in accidents with cranial traumatism, whether traffic (the majority), workplace or domestic. The psychoneurological tests and brain damage (by MR) correlate better than bulbar volumetry (by MR) with the affectation of the sense of smell despite not predicting its capacity for recovery by smell training. Finally, smell training can be considered a beneficial type of therapy in improving smell performance although recovery is slight and is linked to continual training.

II. ANIMAL MODEL of OB lesion with NMDA of in rats (IDIBAPS):

1. The animals with bilateral lesion of the OB induced by administration of the glutamatergic agonist NMDA present olfactory dysfunction and a restructuring of the cellular layers of the OB associated to a decreased volume of the OB, as well as changes in neurogenesis in the subventricular zone.

2. Smell training has a positive effect by causing an increase in the percentage of correct responses in the smell test, faster smell discrimination and a fall in the number of errors in lesioned rats with olfactory dysfunction.

3. The treatment at low doses of MK801, antagonist of the NMDA receptors, has a beneficial effect, improving the olfactory dysfunction, increasing the percentage of correct responses and decreasing the time that the animals spend recognising the smell.

4. The administration of NMDA to cellular cultures of OB produces cell death in the different cell populations of the OB, similar to those obtained in the in vivo model.

FINAL CONSIDERATION. The excitotoxicity induced by the bilateral intrabulbar administration of the glutamatergic agonist NMDA in the rat provides a good experimental model for studying the olfactory dysfunction produced due to the excess of glutamate release after a TBI in humans. This model allowed us to know some of the mechanisms involved in this olfactory dysfunction, such as the changes in the neurogenesis of the subventricular zone, and to confirm, as has been seen in the clinical study, that the training involves a beneficial effect in recovery from olfactory dysfunction.

3. Relevance and possible implications

1. In the accidents with acute cranial traumatism (TBI), whether traffic (the majority), workplace or domestic, the loss of smell is manifested much more frequently (4 out of 10 cases). The psychoneurological tests and the MR score, but not the volume of the olfactory bulbs, can be used to diagnose the severity of the TBI, although they can

hardly be predictive of the improvement in the sense of smell, whether spontaneously or with smell training.

2. The study of the effect of excitotoxicity induced by the glutamatergic agonist NMDA in the OB in the experimental model in rat gave us deeper knowledge of the biochemical, histological and molecular mechanisms that are involved in the olfactory dysfunction that takes place in TBI in humans.

3. This experimental animal model also allowed us to know the importance of smell training in the improvement that can occur in the olfactory dysfunction associated to TBI in humans, showing clear that smell training could be the best therapeutic strategy in these patients.

4. The results clearly show the relevance of neurogenesis in recovery from olfactory dysfunction in humans, which will make it possible to go ahead and open up new research lines connected with new treatments that favour this process and will be beneficial for the clinical treatment of olfactory dysfunction in the TBI in humans.

5. Obtaining the cultures of OB cells makes it possible to open a new research line to test drugs that could be selective neuroprotectors of the different cell populations that can be cultivated and that would have a clinical benefit in the prevention of neuronal death in TBI in humans.

6. So, smell training or rehabilitation in patients with TBI and loss of smell can be considered as a type of therapy (if not the only current one) that is effective and beneficial in improving olfactory performance, even though this recovery is slight and possibly linked to continual smell training. The marketing and possible patenting of a battery of 6 odorants (BASTAT-6) to facilitate smell rehabilitation in patients with TBI and loss of smell is also an important achievement of this project.

7. Finally, the multidisciplinary collaboration (neuroscientists, rehabilitation doctors, ENT specialists and basic researchers) in the management of these patients with TBI is fundamental with respect to the information about smell loss in the framework of traumatic cranial injury and on the possibilities of recovery, spontaneous or by smell training.

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