Pain as a Risk Factor For Alzheimer’s Dementia

Rev. Dr. Mizraim Esquilín-García
Iglesia AMEC: “Casa de Alabanza”
Puerto Rico
A proposal and a challenge that seeks three main objectives

- The need to increase the way we, as care providers and researchers, issue better and more responsible means for the problem of pain in our patients.
- To provoke the attention of the research and caregiver’s communities to the subject of pain as a key factor in the AD development
- To foster interdisciplinary approaches to AD as paramount to this disease
Approaches to AD
Structure of the PRNP protein.

Based on PyMOL rendering of PDB
Creutzfeldt-Jacob disease: History

- **The Kurus**: The Forest People: the Purari side of the Ramu Purari Divide in New Guinea
- Dr. Carleton Gajdusek, 1957, Dr. Joseph Smadel (NIH, Bethesda Maryland)
- In 1966 they prove that it is an infectious disease ("Spongiform encephalopathy")
Creutzfeldt-Jacob

- In 1967 John Stanley Griffith (Biophycist from Beford College) propose that it may be caused by a protein.
- Stanley Ben Prusiner and colleagues isolated it on 1990 (UCalifSFco); PrionP (Nobel Prize)
Some mechanisms explained

- **Creutzfeldt-Jakob disease** - glutamic acid-200 is replaced by lysine while valine is present at amino acid 129.

- **Gerstmann-Sträussler-Scheinker syndrome** - usually a change in codon 102 from proline to leucine

- **Fatal familial insomnia** - aspartic acid-178 is replaced by asparagine while methionine is present at amino acid 129.
Structure of the PRNP protein.

Based on **PyMOL** rendering of PDB
The human PRNP gene is located on the short (p) arm of **chromosome 20** between the end (terminus) of the arm and position 12, from **base pair** 4,615,068 to base pair 4,630,233.
Previous experiences
1998

- Dr. Jordi Alom Poveda
- General University Hospital
  Elche, Alicante, Spain
  Neurology Section

- First Iberoamerican Virtual Congress of Neurology, Oct 1998

http://www.uninet.edu/neurocon/congreso-1/conferencias/priones-5.html
In recent years we have a variety of clinical patterns with prionc ethiopatogenesis. This have widen the clinical spectrum of these diseases:

- Dementia with Tropical Spastic Paraparesis (TSP)
- Thalamic dementia
- Spongiform Encephalopathy
- Progressive Subcortical Gliosis
"At the same time, cases described as Family Alzheimer’s disease has been re-explored and classified of Prionic Origin…” (Free translation)
Cellular Prion Protein Mediates Impairment of Synaptic Plasticity by Amyloid-β Oligomers

Juha Laurén, David A. Gimbel, Haakon B. Nygaard, John W. Gilbert, and Stephen M. Strittmatter

- Cellular Neuroscience, Neurodegeneration & Repair Program, Yale University School of Medicine, New Haven, CT 06536, USA
- Nature. Author manuscript; available in PMC 2009 September 22. Published in final edited form as: Nature. 2009 February 26; 457(7233): 1128–1132.
“Here, we identify the cellular Prion Protein (PrP\textsuperscript{C}) as an Aβ-oligomer receptor by expression cloning. Aβ-oligomers bind with nanomolar affinity to PrP\textsuperscript{C}, but the interaction does not require the infectious PrP\textsuperscript{Sc} conformation.” Juha Lauren, et al
Anti-PrP antibodies prevent Aβ-oligomer binding to PrP<sup>C</sup> and rescue synaptic plasticity in hippocampal slices from oligomeric β. Thus, PrP<sup>C</sup> is a mediator of Aβ-oligomer induced synaptic dysfunction, and PrP<sup>C</sup>-specific pharmaceuticals may have therapeutic potential for Alzheimer’s disease.

Juha Lauren, et al
Oligomeric Aβ42 binds to neurons and to cells expressing PrP^C

Juha Lauren, et al
Fibrillar Aβ

Juha Lauren, *etal*
Hippocampal Oligo Aβ

Juha Lauren, et al
The mechanism by which Aβ42-oligomer binding to PrP<sup>C</sup> participates in AD appears unrelated to the infectious PrP<sup>Sc</sup> conformation of PrP. In this regard, the neurodegeneration reported in transgenic mice expressing truncated forms of PrP<sup>C</sup> may be more relevant<sup>17,18</sup>. A putative PrP<sup>C</sup>-associated transmembrane co-receptor is likely to play a central role in AD-mediated neurodegeneration. PrP<sup>C</sup>-specific reagents will provide molecular tools to dissect the cellular basis for Aβ42-oligomer induced changes in synaptic function. The interaction between Aβ and PrP<sup>C</sup> provides a novel site for the development of therapeutics designed to relieve AD symptoms.
Sustained translational repression by eIF2α–P mediates prion neurodegeneration

Julie A. Moreno¹, Helois Radford¹, Diego Peretti¹, Joern R. Steinert¹, Nicholas Verity, et al

Nature. ; 485(7399): 507–511. doi:10.1038/nature11058
Available in PMC 2012 June 19
The cellular prion protein traps Alzheimer’s A_ in an oligomeric form and disassembles amyloid fibers

Nadine D. Younan,* Claire J. Sarell,* Paul Davies,† David R. Brown,† and John H. Viles*,

The FASEB Journal • 2013 Jan 30
FIRST REASON
Involvement of cellular prion protein in the nociceptive response in mice.

- Meotti FC, Carqueja CL, Gadotti Vde M, Tasca Cl, Walz R, Santos ARF.

- Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS, 97110-000, Brasil.
Abstract

The role of the cellular prion protein (PrP(c)) in neuronal functioning includes neuronal excitability, cellular adhesion, neurite outgrowth and maintenance. Here we investigated the putative involvement of the PrP(c) function on the nociceptive response using PrP(c) null (Prnp(0/0)) and wild-type (Prnp(+/+)) mice submitted to thermal and chemical models of nociception.
Cellular prion protein protects from inflammatory and neuropathic pain

- Gadotti and Zamponi, Molecular Pain 2011, 7:59
  - http://www.molecularpain.com/content/7/1/59
    - doi:10.1186/1744-8069-7-59

- Department of Physiology and Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary T2N 4N1, Canada. Scientist of the Alberta Heritage Foundation for Medical Research and a Canada Research Chair in Molecular Neurobiology.
Abstract

- **Cellular prion protein (PrPC) inhibits N-Methyl-D-Aspartate (NMDA) receptors.** Since NMDA receptors play an important role in the transmission of pain signals in the dorsal horn of spinal cord, we thus wanted to determine if

- PrPC null mice show a reduced threshold for various pain behaviours.

- We compared nociceptive thresholds between wild type and PrPC null mice in models of inflammatory and neuropathic pain, in the presence and the absence of a NMDA receptor antagonist.
Figure 8.8 Ionotropic glutamate receptors.
Data that have to be considered

- NMDA receptors are the critical glutamate receptors triggering storage of new memories²

SECOND REASON
Second Reason
Pastoral and caregiver point of view

- AD patients history encoded different kinds of pain problems that, generally speaking, were not necessarily managed as needed.
- The majority of these pain experiences were suffered for extended period of times.
- Most of these pain experiences can be related to the Central Pain Pathways.
The problem of Pain

- The International Association for the Study of Pain has given the following definition:

  “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”

The problem of Pain

- This definition emphasizes the affective (emotional) component of pain. Its other component is sensory-discriminative (‘Where and how much?’).
The problem of Pain

- Pain neurons are not located in our brain. Pain neurons are squeezed between each vertebra of the spinal column;
  - one sack of pain neurons on each side of the spinal column at each segment of the spine.

- Every neuron from a particular sensory nerve sack has its own sharply defined domain of the body\(^1\)

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The problem of Pain

- We have to study Pain Pathways.
- Studying Peripheral Pain Pathways we find that pain is served by finely myelinated \((A\delta)\) and unmyelinated \((C)\) fibers belonging to unipolar spinal ganglion cells.
- These fibers are loosely known as ‘pain fibers.’

The Problem of Pain

- We have to study Central Pain Pathways.

Ibid. Chapter 15
The Problem of Pain

Experts in this field says that describing the Central Pain Pathway is really to describe two pathways:

- Lateral, *sensory-discriminative pathway* and a
- Medial, *affective pathway* in relation to pain

Ibid. Chapter 34
Lateral Pain Pathway

➢ For the trunk and limbs,
  • the lateral pathway arises in the posterior gray horn of the spinal cord and projects as the lateral spinothalamic tract to the posterior part of the contralateral ventral posterior lateral nucleus of thalamus.

➢ For the head and neck,
  • it commences in the spinal nucleus of the trigeminal nerve and occupies the trigeminothalamic projection to the contralateral posterior medial thalamic nucleus.

Ibid. Chapter 34
Medial Pain Pathway

➤ Medial pain pathway

➤ The medial pathway is polysynaptic, via spinoreticular and trigeminoreticular tracts to the contralateral medial dorsal thalamic nucleus (among others), with onward projection to the anterior cingulate cortex.

➤ One of the most important facts about this pathway is that this area is concerned with the affective component of pain experience

Ibid. Chapter 34
Dealing with Central Pain States

- We have to study Central Pain States.
- These states are almost always generated by Wind-Up of the CPPNs (Central pain-projecting neurons) of the spinothalamic and spinoreticular pathways.
One of the mechanisms that may be responsible:

- Repetitive activation of NMDA glutamate receptors by posterior nerve root inputs, over a period of weeks or months, tends to induce a state of long-term potentiation of CPPNs.

Chapter 34
Figure 8.8  Ionotropic glutamate receptors.
Data that have to be considered

- The fibers that NMDA receptors support are not insulated.\(^1\)
- Their velocity of conduction will be 100 times slower
- PrionP’s time of exposure will be extended.

<table>
<thead>
<tr>
<th>Nerve type</th>
<th>Number</th>
<th>Letter</th>
<th>Diameter (µm)</th>
<th>Conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>I</td>
<td>Aα</td>
<td>12–20</td>
<td>70–120</td>
</tr>
<tr>
<td>Medium</td>
<td>II</td>
<td>Aβ</td>
<td>6–12</td>
<td>35–70</td>
</tr>
<tr>
<td>Small</td>
<td>III</td>
<td>Aγ</td>
<td>3–6</td>
<td>10–40</td>
</tr>
<tr>
<td>Small</td>
<td>–</td>
<td>Aδ</td>
<td>2–5</td>
<td>5–35</td>
</tr>
<tr>
<td>Unmyelinated</td>
<td>IV</td>
<td>C</td>
<td>0.2–1.5</td>
<td>0.5–2</td>
</tr>
</tbody>
</table>

Table 9.1 Classification of peripheral nerve fibers
FitzGerald, M. J. T.; Gruener, Gregory; Mtui, Estomih (2011-04-14).
Clinical Neuroanatomy and Neuroscience
Other data that have to be considered

- Prion P becomes resistant to attack by folding into new, impervious shape

- In 2005 it was reported that normal PrionP is found in purified myelin and in oligodendrocytes

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What do we know?

- Cellular PrionP traps Alzheimer's Aβ in an oligomeric form.
- An antibody of this protein has been isolated as part of its role mediating the impairment synaptic plasticity of Amyloid-β Oligomer.
  - The isolation of this antibody may be a key factor for AD research
- History of AD patients with previous pain experiences
What do we know?

- NMDA receptors triggers the storage of new memories
- NMDA receptors are activated by the Wind-Up of the CPPNs (Central pain-projecting neurons)
- PrionP has been identified in both, the mechanism of AD and in pain pathways.
Conclusion

There may be a relation between this version of PrionP and the extended time of exposure assisting the repetitive activation of NMDA glutamate receptors.
Conclusions

- To encourage the communities of researchers to identify the PrionP’s proteinic link that interacts with the NMDA receptors.
- To increase the caregivers and medical provider’s attention to pain’s management. Thus, a preventative measure facing the probability of a significant reduction of future AD incidence.
Interdisciplinary approach

Where does spirituality fit into this subject?


- Spirituality can bring about mood changes, creating a sense of peace (Phinney 1998) or the feeling of “let go and let God” Belluck, Pam. December 31, 2010. “Giving Alzheimer’s patients their way, even chocolate.” New York
AD patients remember:

- Songs (specially with religious backgrounds)
- Prayers
- Significant Religious Texts
- It has been theorized that they help lowering cortisol levels
Pastoral and caregiver point of view

High levels of Cortisol in AD patients

- “Cortisol Levels in Alzheimer’s Patients are related to Premorbid Functioning and Rate of Progression” (Feb 11, 2011)
  - Paul J Massman, Christina Burrows, James Hal, Rachel S Doody.
  - Univ of Houston, Baylor College of Medicine, Univ Of North Texas.

- American Academy of Neurology (AAN)
  63rd Annual Meeting in Honolulu, Hawaii (April 9-16, 2011)
Summary

- Serum cortisol was significantly higher in AD patients (M=140.9) than in controls (M=126.4). Values were positively skewed, and the group difference persisted when log-transformed values were analyzed. In AD patients, cortisol values were not significantly correlated with any neuropsychological test scores, but were negatively associated with AMNART estimated IQ ($r = -0.20, p<.01$)

- This suggests that cortisol levels may partly contribute to progression in these patients, at least early in the disease. Alternatively, patients who are declining more rapidly may experience greater stress, and therefore exhibit higher cortisol levels.
There is a burgeoning body of research on spirituality and illness, although most is focused on health professional view rather than the patient (Beck 2001).

Chronic illness often provokes a desire to address existential and spiritual issues (Folkman & Greer 2000), especially under circumstances where there is a limit to the impact of biomedicine (Lensyn 2004). But is this true for AD patients who experience severe cognitive decline and loss of identity? Yes.
Spirituality can be a component of organizational behavior such as church attendance, or non-traditional forms such as meditation (Beuscher & Beck 2008).

Research conceptualizes the significance of spirituality in AD in terms of symbolic, relational, emotional, and aesthetic components of coping with the disease. That is, when other aspects of life and the patient’s “self” decline in importance, spirituality remains meaningful because of its role in enabling the patient to connect, feel, sense, and discover meaning in their situation (Stuckey et al. 2002).

In this way, spirituality can be an integral part of coping with AD.
Patients with AD experience disconnection from others (Bahro et al. 1995), including a “loss of self” (Charmaz 1983) that may result in social isolation. Social isolation is linked with feelings of loneliness and depression as well as higher mortality (Hays, Pieper & Purser 2003).

There are negative emotional states that are often unexplainable and can impact behavior and compliance. AD patients have progressive cognitive loss and may be unable to reflect on the past or project into the future (Sloane et al. 2002).

Finally, they experience role loss and confusion (Matano 2000), which can disrupt their sense of coherence about the world (Anonovksy 1987).
Synaptic Dysfunction

- How beta-amyloid interferes with memory formation