NGF-PC-AD CONNECTION

*Some men see things as they are and say: 'Why?'
I dream things that never were and say: 'Why not!'*

John F. Kennedy

In an elegant manner Viviana Triaca presented in this volume of *Adipobiology* her Homage to Rita Levi-Montalcini highlighting the significance of nerve growth factor (NGF) in the molecular mechanisms of Alzheimer's disease (AD) (1, also see Note in the References). This remarkable review generates a completely new direction in understanding some of the new and specific aspect of AD pathology, focusing on the NGF modulation of amyloid precursor protein (APP) processing and metabolism. Dr Triaca provides a paradigm shift from "classical" cholinergic to NGF-centered approach showing that the dysregulation of NGF-TrkA (receptor tyrosine kinase A) and proNGF-p75^{NTR} signalling systems is a good candidate for being *primus movens* in the pathogenesis of AD (1).

Here we spotlights the possible involvement of primary cilium (PC) and PC-associated NGF signaling in the pathogenesis of AD.

As often occurs in the history of biomedical sciences, the presence or even the existence of a newly discovered cellular structure has been "enjoyed" a traditional neophobia. This was also the case with the PC. Hence within the last 15 years the emerging evidences have been demonstrating that in addition to their well-established roles in sight, smell, and mechanosensation, PC is a signaling hub for many physiologically, developmentally and diseased processes (2-5).

Almost all cells in the human body contain a single, primary cilium (PC). Cilia are plasma membrane-microtubule organelles represented by two major phenotypes: (i) motile, 9 + 2 cilia, nu-

merous per certain populations of cells, and (ii) non-motile, primary, 9 + 0 cilia, single per almost all cell types including the neurons (2-5).

Although PC were observed around 1897 by Zimmerman in the renal epithelial cells (cited in 4), conclusive evidence of their existence required the introduction of the electron microscope for biological studies (6-8). Primary cilia control multiple cellular processes (9-14) such as fluid mechanical forces, calcium channel functioning, protein trafficking, and receptor-mediated signal transduction (15 for PC-p75^{NTR} connection). For the pioneering contributions of Poole and colleagues to cilium as cellular "cybernetic probe" functioning *via* its association with the Golgi complex, see 16,17, also 18.

The unprecedented interest in PC research came after the discovery that PC dysfunction or aciliogenesis is the culprit for many disorders now collectively termed *primary ciliopathies*, a selected list presented in Table 1. Intriguingly, various neuropsychiatric diseases including Alzheimer's disease (19-21) were recently also included in the list. In the same vein, obesity is a disorder associated with ciliopathies, such as Bardet-Biedl syndrome and Alström syndrome (22). And leptin, a prototypic adipocyte-secreted protein (adipokine), was implicated in obesity-associated ciliary dysfunction (23). Since obesity patients are prone to the development of AD, and APP is expressed also in the adipose tissue (24), these data may further implicate PC dysfunction in AD neurodegeneration.

Noteworthy, neurons contain both multiple spines on their dendrites as well as PC emanating from their soma. It was suggested that similar to dendritic spines (DS), another plasma membrane-cytoskeletal organelle (25), PC may function like a postsynaptic structure specialized in responding to “presynaptic” environmental stimuli (26,27). Moreover, the formation and plasticity of DS require (i) brain-derived neurotrophic factor (BDNF), the first cousin of NGF, and (ii) not only actin and associated proteins, but also microtubules (28).

As mentioned above, PC expressing the panneurotrophin receptor p75^{NTR} has been found in AD-associated granule cells of the adult hippocampal dentate gyrus in mice (15, see also 19-21,29). Since amyloid beta has been shown to bind p75^{NTR} and

induce apoptotic pathway in neurons (1), PC-p75^{NTR} connection might be implicated in the amyloid beta-driven neurodegeneration of AD (see 1 for IGF1 involvement in APP processing, and 30 for PC-IGF1 link).

As Dr Triaca notably states, a focus shift to “the discovery of blood or cerebrospinal fluid markers for early diagnosis, and early therapeutic intervention with modulators of APP processing” is a sign that the dynamics of AD research is undergoing remarkable plasticity. We expect that the next several years will delivered new insights into the significance of these amazing cellular molecules (NGF, p75^{NTR}, BDNF and IGF1) and organelles (PC and DS) in the pathogenesis of AD.

Why not!

Table 1. Selected disorders shown in >200 reports published in 2013*

1. Retinal dystrophy and degeneration	Many types
2. Neonatal and fetal death	A multitude of disorders
3. Bardet-Biedl syndrome(s)	Mesoaxialpolydactyly
4. Polycystic kidney disease and injuries	Autosomal dominant and recessive
5. Motor neurone disco-ordination	
6. Pre-invasive and invasive prostate cancer	
7. Joubert syndrome	Absence of well-formed cilia
8. Meckel-Gruber syndrome	
9. Nephronophthisis	Multi-organ dysgenesis
10. Lowe syndrome	Brain malformations
11. Biliary atresia	
12. Alström syndrome	
13. Cardiometabolic diseases	Obesity, insulin resistance
14. Mental retardation	Atherosclerosis, obesity, diabetes
15. Ventricular septal defects	
16. Jeune, Sensenbrenner, and Mainzer-Saldino chondrodysplasia	
17. Lens fiber differentiation	Disorientation of fibers
18. Cholangiocarcinoma	
19. Renal carcinoma	
20. Meier-Gorlin syndrome	
21. Birt-Hogg-Dube syndrome	
22. Alzheimer's disease	
	NGF-p75 ^{NTR} -PC link?

* Modified from Wheatley (4).

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