Article 2:

New insights into pathophysiology of dementia

Abstract

Improving understanding of brain disorders seems set to become one of the core applications of physiological research in the 21st century. Cognitive impairment and Dementia are not restricted to older people, but disorders that cause dementia tend to occur in later life so this article explores some of the emerging new insight to underlying pathophysiological processes. Although it is not yet clear whether dementia is the result of accelerated ageing of the brain or separate disease processes, new perspective can be applied to help to explain neurodegeneration in the most common forms of dementia. Better understanding of these mechanisms can help nurses to consider their contribution to behaviours of those who are living with the disease.

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Dementia is an umbrella term for a chronic, progressive syndrome that is characterised by degeneration of the brain (World Health Organisation, 1992). This statement may be something of an oversimplification for challenges of Alzheimer's disease, vascular dementia and neurodegenerative disorders that encompass difficulty in remembering, problems with learning new things, distorted awareness of the passage of time and a gradual loss of ability to make informed decisions (see article 1 of the series).

Some 30 million people around the world live with dementia, which is equivalent to about 4.5% of people over 65 and up to 10% of those aged over 70. In the UK alone, the disease affects approximately 840,000 people – about 7% of people over 65 years (Alzheimer's Society UK, 2014) – with an estimated annual cost of £26 billion which is predicted to rise to over £50 billion in the next 30 years (Dept of Health, 2015. Jenkins et al, 2016).

Public awareness of dementia has grown because the disorder attracts more media headlines, so some people may become fearful that they are imagining symptoms if the normal age-related changes are poorly explained. Others may benefit from simple lifestyle-related advice that promotes successful ageing and may help to prevent dementia (see article 3 of this series). To be alive is to age, but some of the changes that occur in elderly people tend to be perceived as signs of deterioration and decline. Everyone who is involved with provision of care for those who have dementia bears a responsibility to ignore stereotypes of older people and see each person as a unique individual who has a particular set of talents, resources and challenges (see article 4 of this series).

Dementia and neuro-inflammatory processes

The apparently normal alterations in speed and memory that occur with advancing chronological age – "senior moments" - do not usually interfere with activities of daily living. Dementia is not a normal part of ageing but is a disabling condition that is characterized by progressive damage to neurons and their connections (see article 1 of this series). Loss of volume in regions such as the hippocampus, basal ganglia, cerebellum and pre-frontal cortex of the brain can begin as early as the fourth decade (Selkoe, 2001; Linden, 2012).

With a rapidly ageing population, it is imperative to identify modifiable risk and/or protective factors associated with cognitive decline and this is why mechanisms of brain inflammation (neuroinflammation) not caused by infective agents are attracting increasing interest. They are – to an extent – atypical and different from acute or chronic inflammation that occurs elsewhere in the body, but are thought to accelerate loss of neurons and white matter within the brain (Trollor et al, 2012).

Pathophysiology of excitotoxicity.

It is clear that dementia is caused by an interplay between genes, lifestyle and environmental factors (Ferencz and Gerritsen, 2015) but until quite recently, it was generally assumed that death of neurons causes neurotransmitter loss, but alternatively neurotransmitter depletion itself may at least contribute to neurodegeneration. (Alisky, 2006)

Regulation of extracellular concentrations of the neurotransmitter molecule glutamate (Figure 1) seems to be critical for normal brain function, processing speed and cognitive function because it contributes to long-term potentiation and plasticity amongst key neural structures important for memory and learning (Rudy et al, 2015): -

1. Glutamate molecules are packaged into synaptic vesicles before being released from neuron terminals on arrival of depolarizing action potentials.
2. Glutamate binds to NMDA receptors and has an excitatory effect on post-synaptic cells
3. Glutamate is removed from the synapse by neighbouring astrocytes and/or the pre-synaptic neurons (Panatier et al, 2014)

However, nervous tissue dies when too much glutamate is produced by pre-synaptic neurons, or when the ability of astrocytes to clear glutamate from the synaptic cleft is exceeded. Glutamate reaches pathological levels and promotes overstimulation of neurons through a process called excitotoxicity (see figure 2). Uncontrolled levels of glutamate may erode the integrity of vulnerable networks leading to progressive failure of complexly inter-connected neural networks (Stambler, 2015).

Alzheimer's disease (AD)

The characteristic signs of this disorder are progressive loss of memory, declining executive function, difficulty with language and changes in behaviour caused by

neurodegeneration that results from both genetic and environmental factors. AD affects almost 10% of adults over the age of 65 years and is a major cause of death.

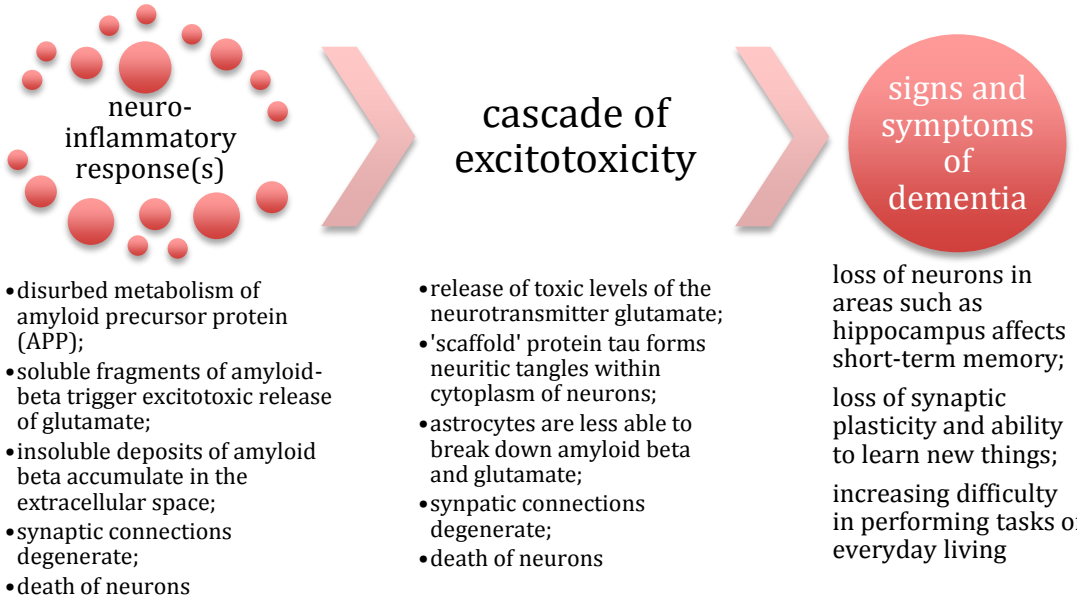
Alzheimer ’s disease is characterised by build-up of abnormal protein structures called “plaques” and “tangles” in many of the brain regions that are typically affected by the disease. The discovery of aggregation and deposition of amyloid-beta (Aβ) in the neuritic plaques and of hypophosphorylated tau protein in the intracellular neurofibrillary tangles led to the so-called amyloid hypothesis. The concept suggested that the abnormal form of amyloid-beta triggered a pathophysiological cascade that led to the disease.

The time taken to develop these lesions is unknown; they probably evolve very gradually over a substantial period of time but it now seems likely that inflammatory processes and glutamate homeostasis are deregulated in Alzheimer’s disease. Inflammatory alterations in the permeability of endothelial tight junctions that create the Blood-Brain-barrier (BBB) further contribute to dysfunctional neuronal networks and, ultimately, to signs and symptoms of dementia (see Figure 3).

The hippocampal circuits of the limbic brain – crucial for memory and learning - are amongst the earliest structures to be affected by degeneration so storage deficits are an important feature of the disease. Orientation to time and place are also disrupted early in the disease. People who have AD may find it difficult to prepare a meal or may ask a question several times – a result of rapid forgetting and poor recall of recent events and conversations. Nurses should expect to repeat what they say several times or allow more time to perform tasks (see article 3 of this series).

There is widespread loss of acetylcholine and other neurotransmitters in Alzheimer’s disease and vascular dementia. Cholinergic neurons in the basal forebrain are lost at an early stage of Alzheimer’s disease but degeneration may be slowed through the use of cholinesterase inhibitors (see article 3) after a diagnosis of dementia has been confirmed.

Figure 2: *a feed-forward cascade of molecular and cellular events lead to the formation of amyloid plaques and neuritic tangles in the brain of people who are affected by Alzheimer’s disease (AD).*



Vascular Dementia (VaD)

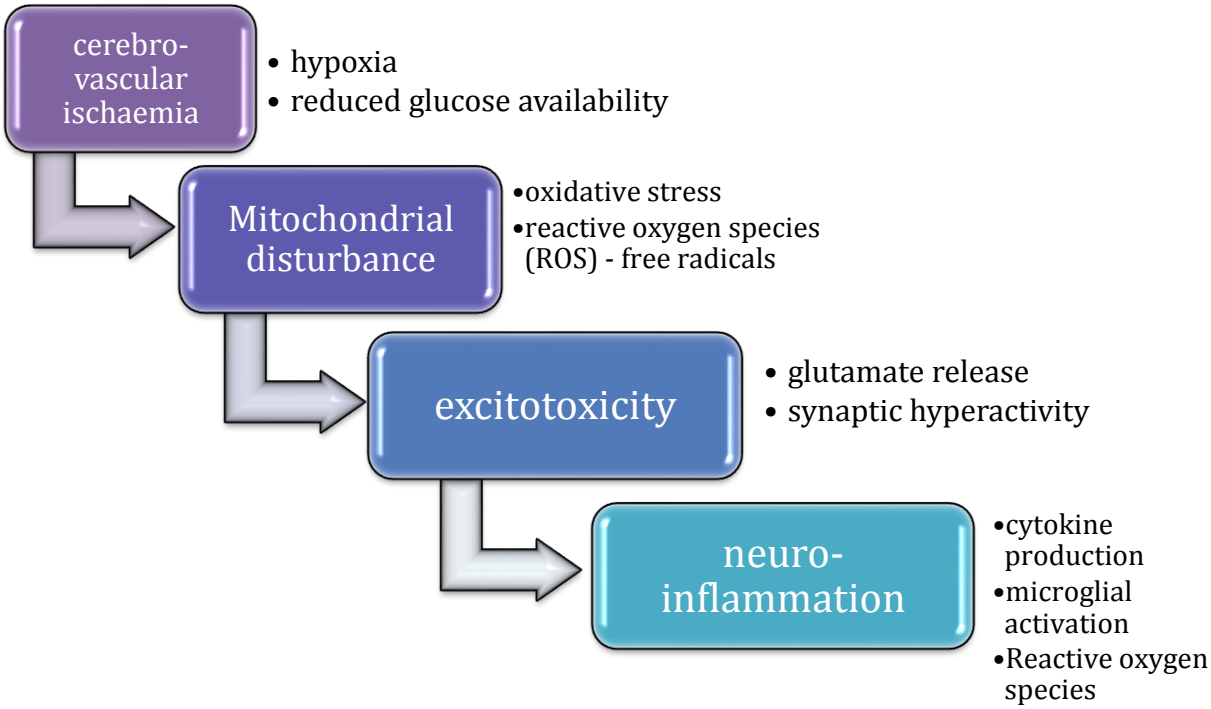
Vascular dementia (multi-infarct dementia) is caused by impaired blood supply to the brain, possibly due to a series of microbleeds, transient ischaemic attacks (TIAs) or cerebrovascular incidents (strokes). Compared to AD, VaD is more often characterized by attention and concentration deficits, slowness of thoughts and word finding problems. However deficits that are experienced by the person depend on the location of cerebrovascular disease so it is a very heterogeneous disease

Focal ischemia and oxygen-glucose deprivation disrupts metabolic processes in mitochondria of brain cells. Cells, including neurons, rely on homeostatic surveillance mechanisms and clearing of toxic intracellular components (Martinez-Vincente and Cuervo, 2007). In response to the hypoxic insult to brain tissue, white cells cross the blood-brain barrier to phagocytose debris but the inflammatory response also increases production of reactive oxygen species (ROS) which further damages neurons (Witte et al, 2010) thus triggering the production of toxic levels of glutamate (see Figure 4). The subsequent pathophysiological cascade contributes to neuron losses and shrinkage of brain tissue (Sas et al, 2010) leading to signs and symptoms of VD.

Deregulated lipid metabolism is emerging as an important risk factor for both stroke and vascular dementia. Human apolipoprotein E (apoE) is an important transporter of cholesterol in the CNS and loss of this function – especially through inheritance of the APOE4 allele – is another potential mechanism for degeneration (Rohn et al, 2014) but which is tackled through the therapeutic use of statins (cholesterol-lowering therapy).

Figure 3 *a pathophysiological cascade is thought to fuel cell death and synaptic*

reorganization in vascular dementia



Dementia with Lewy Bodies (DLB) or Parkinson's disease dementia (PDD).

Lewy bodies are microscopic, inclusion bodies in the cytoplasm of neurons, which are composed of abnormal forms of the proteins ubiquitin and α-synuclein. They form in regions throughout the brainstem, basal ganglia and cerebral cortex. The result is disruption to both cholinergic and dopaminergic pathways in the brain (Ballard et al, 2013; Gore et al, 2015).

People who are affected experience visual disturbance and hallucinations, rapid eye movement sleep behaviour disorder (RBD), attention deficits and marked loss of neurons in the nigro-striatum. Changes in neurotransmitter systems also helps to explain the frequency of psychosis, depression and profound sensitivity to neuroleptic medications (which are dopamine antagonists) amongst the people who have this disorder.

Frontotemporal dementia

Frontotemporal dementia (FTD) refers to a diverse group of conditions that include Pick's disease and which are sometimes misdiagnosed as mental health problems and/or associated with neurological problems. FTD can manifest as distinct subtypes: a behavioural subtype and a language disturbances subtype

About half of the people who are affected present with progressive aphasia (impaired language comprehension) while the remainder experience a distinct profile of symptoms including changes in personality and social behavior, loss of insight and empathy, neglect of responsibilities and diminished ability to self-care.

Hyperphosphorylation of Tau leads to misfolding and formation of aggregates in FTD, but the significance of this protein pathophysiology is still unclear (Tenreiro, Eckermann and Outeiro, 2014)

The average age of onset (52.8 years) of FTD means that the person who is affected, their families and loved ones have a distinctively different and more stressful experience compared with other forms of dementia (Bristow et al, 2008). The nature of the challenges means that carers often report that they feel less competent and have higher levels of distress requiring a great deal of support.

The future of dementia care

The population is ageing with increasing incidence of dementia so new strategies are needed to slow age-related decline in health and reduce disease-related cognitive impairment. Although the causes of dementia are not fully understood, it is clear that progress in molecular biology of neuroinflammation and excitotoxicity are advancing our knowledge of dementia beyond basic descriptions.

The complex challenge of caring for those whose capacity is altered by cognitive impairment will be explored in articles 3 and 4 but it can help to have a sound grasp of the facts when having conversations with people who have dementia and their carers and families. The extent to which the mechanisms described here are involved in neurodegeneration is yet to be established but these processes may catalyse other on-going changes. In article 3, we explore a range of factors that increase the risk for dementia, but modifiable factors that have the potential to protect people from the onset of dementia are also of interest to all who are affected by dementia.

Key Points.

1. The population is ageing and prevalence of dementia doubles with every 5 years so this article explains some of the pathophysiological processes that happen in the brain when dementia develops.
2. The hallmark characteristics of normal ageing include low-grade inflammatory responses, alterations in metabolic processes, increasing frailty and reduced tolerance to physiological stressors - sometimes called “inflamm-aging”
3. Promising insight to common pathways of disturbed homeostasis and the pathophysiology of dementia is emerging so existing models of dementia e.g. the amyloid cascade hypothesis, are reviewed to take account of new understanding of brain processes

4. Improved understanding of neuroinflammation and neurotoxicity can help to explain the progressive nature of dementia and offer promising new approaches to elimination of aberrant homeostasis.
5. Potential therapeutic strategies include inhibition of dyslipidaemias, management of insulin resistance, neutralisation of reactive oxygen species and increased levels of physical activity, which will be discussed in article 2 of this series.

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