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Review

Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease

Velandai Srikanth [b], Annette Maczurek [a], Thanh Phan [b], Megan Steele [a], Bernadette Westcott [a], Damian Juskiw [c], Gerald Münch [a,*]

[a] *Department of Pharmacology, School of Medicine, University of Western Sydney, Campbelltown, NSW, 2560, Australia*
[b] *Department of Medicine, Southern Clinical School, Monash University, Melbourne, VIC, 3800, Australia*
[c] *Department of Biochemistry and Molecular Biology, James Cook University, Townsville, QLD, 4811, Australia*

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Abstract

Alzheimer's disease (AD) is the most common dementing disorder of late life. Although there might be various different triggering events in the early stages of the disease, they seem to converge on a few characteristic final pathways in the late stages, characterized by inflammation and neurodegeneration. In this review, we revisit the hypothesis that advanced glycation endproducts (AGEs) and their receptor RAGE may play an important role in disease pathogenesis. Accumulation of AGEs in cells and tissues is a normal feature of aging, but is accelerated in AD. In AD, AGEs can be detected in pathological deposits such as amyloid plaques and neurofibrillary tangles. AGEs explain many of the neuropathological and biochemical features of AD such as extensive protein crosslinking, glial induction of oxidative stress and neuronal cell death. Oxidative stress and AGEs initiate a positive feedback loop, where normal age-related changes develop into a pathophysiological cascade. RAGE and its decoy receptor soluble RAGE, may contribute to or protect against AD pathogenesis by influencing transport of β-amyloid into the brain or by manipulating inflammatory mechanisms. Targeted pharmacological interventions using AGE-inhibitors, RAGE-antagonists, RAGE-antibodies, soluble RAGE or RAGE signalling inhibitors such as membrane-permeable antioxidants may be promising therapeutic strategies to slow down the progression of AD.

Keywords: Advanced glycation endproducts; Nitric oxide; Alzheimer's disease; Inflammation; β-Amyloid; Glycation; Diabetes; Oxidative stress; RAGE; Soluble RAGE

1. Alzheimer's disease—epidemiology, histopathology and biochemistry

Alzheimer's disease (AD) is the most common cause of dementia. The prevalence of AD doubles every 5 years after the age of 60, with estimates being over 20% in those over 80 years (Yan et al., 1994). Developing pharmacological strategies to improve the quality of life for patients and to minimize the burden on caregivers is therefore an important task for the community. One of the pathological features of AD is the presence of high densities of 'neuritic plaques' in the neuropil of the cerebral cortex and hippocampus. β-Amyloid (Aβ) peptide is one of the main components of neuritic plaques, and this 40–42 amino acid peptide is widely regarded as a major contributor to the neurodegeneration that occurs in AD brains (Behl et al., 1994; Toth et al., 2007). Strong evidence

Abbreviations: Aβ, β-amyloid peptide; AD, Alzheimer's disease; AGEs, advanced glycation endproducts; BACE1, β-secretase; BSA, bovine serum albumin; CAA, cerebral amyloid angiopathy; CML, carboxymethyl-lysine; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; MAP, microtubule associated protein; M-CSF, macrophage-colony stimulating factor; MRPs, Maillard reaction products; MOLD, methylglyoxal linked dimmer; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NFT, neurofibrillary tangles; PKC, protein kinase C; PHFs, paired helical filaments; RAGE, receptor for advanced glycation endproducts; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α.

* Corresponding author at: Department of Pharmacology, School of Medicine, University of Western Sydney, Locked Bag 1797, Penrith South DC, NSW, 1797, Australia. Tel.: +61 2 9852 4718; fax: +61 2 9852 4701.
E-mail address: g.muench@uws.edu.au (G. Münch).

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for the involvement of Aβ comes from studies of early onset AD, which is inherited in an autosomatic dominant fashion, and in many afflicted families is associated with mutations in the amyloid precursor protein or the secretases that cleave it (Haass et al., 1994; Lichtenthaler et al., 1997; Takeuchi and Yamagishi, 2008). Other characteristics of AD are the intracellular accumulation of neurofibrillary tangles in pyramidal neurons, a local inflammatory process around the amyloid plaques and diminished glucose uptake and utilization in the brain (Schmidt et al., 2005). A direct link between all these phenomena is not established yet, and the discussion continues on whether AD is rather a syndrome with multiple independent pathologies developing at the same time in the aging brain or a disease with a single cause. Ten years ago, it was proposed that the chemical process which may be responsible for both, the observed extensive protein crosslinking and inflammation in AD, is the excess level of free radicals and reactive carbonyl compounds, leading to the formation of advanced glycation endproducts (AGEs) or advanced lipoxidation endproducts (ALEs) (Münch et al., 1997a,b).

2. Chemistry of advanced glycation endproducts (AGEs)

Oxidative stress is defined as an imbalance of radical production and detoxification. DNA oxidation products, such as 8-oxoguanosine, or protein oxidation products, such as dityrosine, are markers of oxidative stress and accumulate during aging and diseases correlated with inflammation (Vitek et al., 1994). In analogy, AGEs (and ALEs) are markers of carbonyl stress, which accumulate due to an increased level of sugars and reactive dicarbonyl compounds such as glucose, fructose, deoxyglucose, glyoxal, methylglyoxal and triosephosphates (Brownlee, 1995; Thornalley, 2003). AGE formation can also commence when amino groups of proteins, particularly the N-terminal amino group and side chains of lysine and arginine react non-enzymatically with these reactive carbonyl compounds. This post-translational modification, termed 'non-enzymatic glycosylation', 'glycation' or 'Maillard reaction', leads via reversible Schiff-base adducts to protein bound Amadori products. Through subsequent oxidations and dehydrations, including free radical intermediates, a broad range of heterogeneous fluorescent and yellow-brown products with nitrogen- and oxygen-containing heterocycles are formed, the so-called AGEs (Fig. 1). These latter reactions are accelerated by transition metals, such as copper and iron, which oxidize the protein-bound Amadori products or the monosaccharides directly in solution (Cochrane and Furth, 1993; Loske et al., 1998). Among physiologically relevant sugars, glucose is the least reactive, presumably the reason for its selection by evolution as the main biological energy carrier; the rank order of reactivity for the

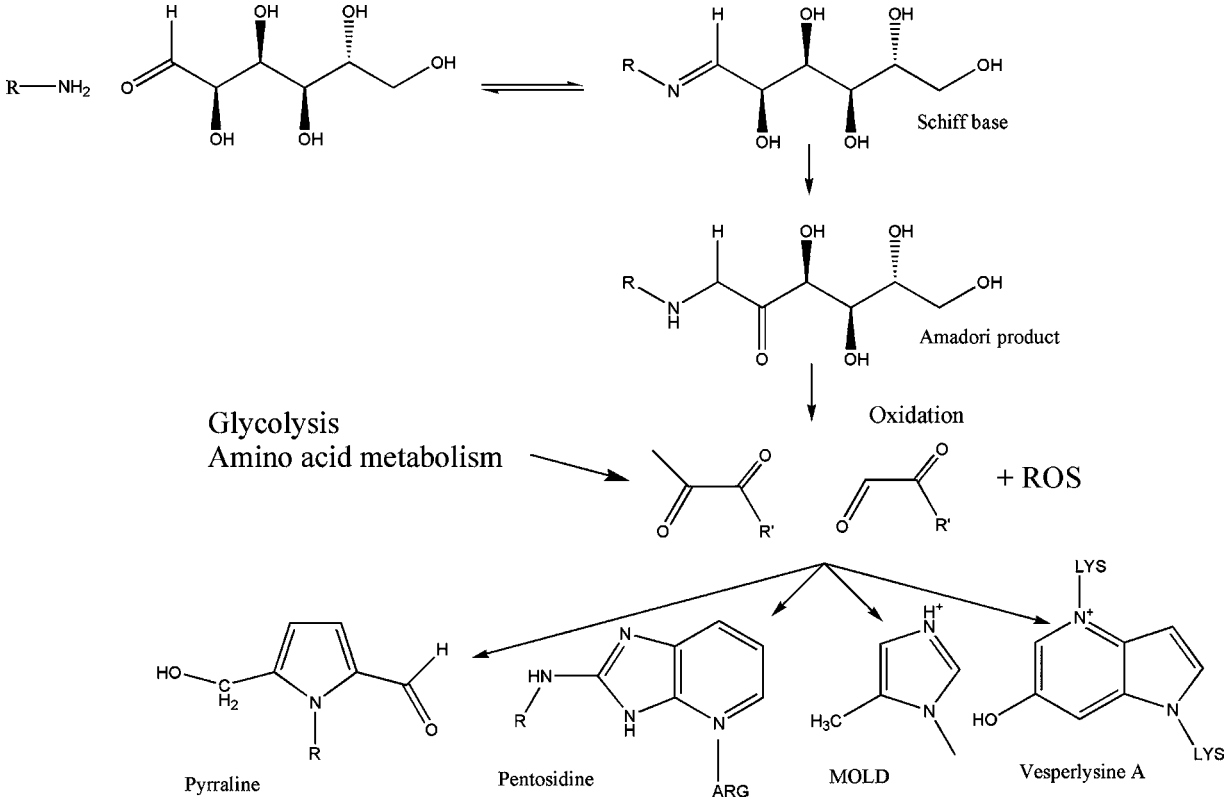

Fig. 1. Formation of advanced glycation endproducts on proteins. Arginine and lysine residues of proteins react with reducing sugars to form the Schiff base, which is rearranged to an Amadori product and finally, after oxidations, dehydrations and other rearrangements leads – via dicarbonyl compounds such as methylglyoxal – to the formation of (often crosslinked) advanced glycation endproducts (adapted from Münch et al., 1997a,b).