Journal of Neural Transmission (2022) 129:755–771
https://doi.org/10.1007/s00702-022-02480-x

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Pharmacological considerations for treating neuroinflammation with curcumin in Alzheimer's disease

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Received: 18 February 2022 / Accepted: 19 February 2022 / Published online: 16 March 2022

Abstract

Prof. Dr. Peter Riederer, the former Head of the Neurochemistry Department of the Psychiatry and Psychotherapy Clinic at the University of Würzburg (Germany), has been one of the pioneers of research into oxidative stress in Parkinson's and Alzheimer's disease (AD). This review will outline how his scientific contribution to the field has opened a new direction for AD treatment beyond "plaques and tangles". In the 1990s, Prof. Riederer was one of the first scientists who proposed oxidative stress and neuroinflammation as one of the major contributors to Alzheimer's disease, despite the overwhelming support for the "amyloid-only" hypothesis at the time, which postulated that the sole and only cause of AD is β-amyloid. His group also highlighted the role of advanced glycation end products, sugar and dicarbonyl-derived protein modifications, which crosslink proteins into insoluble aggregates and potent pro-inflammatory activators of microglia. For the treatment of chronic neuroinflammation, he and his group suggested that the most appropriate drug class would be cytokine-suppressive anti-inflammatory drugs (CSAIDs) which have a broader anti-inflammatory action range than conventional non-steroidal anti-inflammatory drugs. One of the most potent CSAIDs is curcumin, but it suffers from a variety of pharmacokinetic disadvantages including low bioavailability, which might have tainted many human clinical trials. Although a variety of oral formulations with increased bioavailability have been developed, curcumin's absorption after oral delivery is too low to reach therapeutic concentrations in the micromolar range in the systemic circulation and the brain. This review will conclude with evidence that rectally applied suppositories might be the best alternatives to oral medications, as this route will be able to evade first-pass metabolism in the liver and achieve high concentrations of curcumin in plasma and tissues, including the brain.

Keywords Glycation · Curcumin · Dementia · Inflammation · Brain · Suppositories

Chronic neuroinflammation and its role in Alzheimer's disease (AD)

Multiple sclerosis has long been recognized as the "classical" neuroinflammatory disease (Datta et al. 2017).

About 20 years ago, the term 'neuroinflammation' started to be applied to chronic, central nervous system (CNS)-specific, inflammation-like glial responses that do not reproduce the classic characteristics of inflammation but cause neurodegeneration including those observed in Alzheimer's disease (AD) (Eikelenboom et al. 2000; Bales et al. 2000). Chronic microglial activation (T-cell independent neuroinflammation) has been described in many neurodegenerative diseases such as chronic traumatic encephalopathy (CTE), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) (Zhang and Jiang 2015; Faden and Loane 2014; Evans et al. 2013; Fan et al. 2014).

In early immunohistochemical studies in post-mortem tissue of AD patients, Edith and Patrick Lucey "Pat" McGeer, Canadian researchers from the University of British Columbia were one of the first pioneers in the investigation of neuroinflammation in neurodegenerative diseases including AD. Already in the late 1980s, they

Dedicated to Prof. Riederer's 80th birthday.

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detected large numbers of human leucocyte antigen DR (HLA-DR)-positive reactive microglia (macrophages), along with Lewy bodies and free melanin, in the substantia nigra of with PD and Parkinsonism with dementia patients, and less extensive, pathology in the substantia nigra of the AD patients compared to non-demented controls. AD cases showed a large number of HLA-DR-positive reactive microglia (together with plaques and tangles) in the hippocampus, as well as reduced cortical choline acetyltransferase activity. These data indicate that HLA-DR-positive reactive microglia is a sensitive index of neuropathologic progression (McGeer et al. 1988).

As for markers of microglial activation, further studies have identified the “major histocompatibility complex II (MHC II)” protein (or its mRNA) (Parachikova et al. 2007), as well as “cluster of differentiation 68” (CD 68) to be upregulated in AD post-mortem tissue (Arends et al. 2000). Other common markers characteristic for both resting and activated microglia, such as ionized calcium-binding adaptor molecule 1 (IBA 1), particularly around amyloid deposits has also been shown to be elevated in AD patients compared to age-matched controls (Streit et al. 2018).

Another marker of neuroinflammation (e.g. in HIV encephalitis, AD, multiple sclerosis and stroke) is the 18 kilodalton translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor (Parola et al. 1993). TSPO is located on the outer mitochondrial membrane and is involved in cholesterol transport (thereby maintaining neurosteroid biosynthesis) (Papadopoulos et al. 2006), modulating the immune response (Venneti et al. 2006) as well as energy production (Liu et al. 2017). TSPO is a marker of activated microglia and astroglia, endothelial and smooth muscle cells, intravascular monocytes, and ependymal cells (Cosenza-Nashat et al. 2009).

Studies of TSPO expression in post-mortem tissue of AD patients have indicated no difference between AD and age-matched controls, but these investigations only looked at the expression in the final stage of the disease (Xu et al. 2019). The use of TSPO position emission tomography (PET) ligands has allowed mapping not only the spatial distribution but also to reveal the time course of neuroinflammation in AD patients. Following the time course of neuroinflammation in AD progression, there is an initial longitudinal reduction in microglial activation in subjects with mild cognitive impairment, while subjects with AD show an increase in microglial activation. It is suggested that microglia in mild cognitive impairment initially turn into a protective phenotype, which later changes to a pro-inflammatory phenotype as the disease progresses (Fan et al. 2018).

Microglia: morphological studies show multiple states of activation

Microglia were conventionally divided into "HM" (homeostatic), "M1" (classically activated pro-inflammatory), or "M2" (alternatively activated).

M1-type microglia can produce reactive oxygen species (ROS) as a result of NADPH oxidase activation (respiratory burst), and nitric oxide (NO) as a product of inducible NO synthase (in rodents, in humans, astroglia take over this function). Those radicals (and their product peroxynitrite) cause direct inflammatory tissue damage and necrosis. Furthermore. M1 microglia produce pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β. M1-type pro-inflammatory markers are also induced when cultured macrophages and microglia are activated with a combination of lipopolysaccarides (LPS) and interferon (IFN)-γ (Raju et al. 2016).

M2 type microglia are a different type of activated microglia and are considered as the anti-inflammatory response phenotype, contributing to tissue repair and neuroprotection. The M2 phenotype has been expanded to three different subtypes, termed M2a, M2b, and M2c (Franco and Fernandez-Suarez 2015). M2a microglia can be induced by the activation with IL-4 or IL-13. Their characteristics include increased phagocytosis and the production of insulin-like growth factor-1 and anti-inflammatory cytokines including IL-10. The function of M2a microglia is most likely to remove cellular debris and promote tissue regeneration (Franco and Fernandez-Suarez 2015). M2b (also termed: type II alternative activation) is induced by binding of immunoglobulin Fc gamma receptors (FcγRs) (CD16, CD32, or CD64) by immune complexes on LPS or IL-1β primed microglia/macrophages. This type of activation results in reduced expression of IL-12 and increased expression of HLA-DR and IL-10. The M2b phenotype is also characterised by increased expressions of CD32 and CD64, associated with an increased phagocytic activity (Franco and Fernandez-Suarez 2015). The switch to an M2c phenotype (acquired deactivation) can be induced by the anti-inflammatory cytokine IL-10 or glucocorticoids. This leads to an expression of transforming growth factor (TGF) beta, sphingosine kinase (SPHK1), and CD163, the membrane-bound scavenger receptor for haptoglobin/hemoglobin complexes (Franco and Fernandez-Suarez 2015).

It has been suggested that switching the microglial activation phenotype from M1 to M2 could be a possible treatment for neuroinflammatory conditions including depression (Zhang et al. 2018), intracerebral hemorrhage (Xi et al. 2021), and Alzheimer’s disease (Varnum and Ikezu 2012).

Microglia and their phenotypes in mouse models of AD

In the AD brain, microglia show a distinct M1 phenotype, with M1 markers such as IL-1β, IL-6, TNF-α, and inducible nitric oxide synthase (iNOS) being upregulated (Boche et al. 2013). However, these markers (cytokines especially) are short-lived molecules, and therefore might be unreliable in human AD post-mortem tissue considering the conditions antemortem (e.g., infection/hypoxia) and post-mortem conditions (post-mortem interval of many hours before collection). Therefore, more precise studies about microglial phenotypes characteristic for AD have been conducted in transgenic animal models, where the brains can be harvested minutes after death.

Microglial activation and its link to plaques and its major component, β-amyloid

As a characteristic example, APPPS1 mice (a transgenic mouse model of cerebral amyloidosis expressing human amyloid precursor protein (APP) with the Swedish mutation (KM670/671NL) and human mutated presenilin-1 (PS1)-L166P)) exhibit two very distinct morphological microglial phenotypes: cells close to the plaques exhibit "reactive"/amoeboid-like (M1 type) phenotype compared to the rest of the brain where microglia show a homeostatic-type (M0 type morphology (Krabbe et al. 2013). In a similar AD mouse line (APPswe/PS1dE9 mice), microglial activation and increase in oxidative stress start at 12 months of age. In these mice, the microglial phenotype was also examined, including pro-inflammatory cytokines (M1 microglial markers), M2 microglial markers, and suppressor of cytokine signaling (SOCS) family proteins. Interestingly, the microglia in the APPswe/PS1dE9 mice exhibited an M1-like phenotype, mostly expressing TNF-α. Furthermore, microglia in APPswe/PS1dE9 mice also expressed SOCS3 (Iwahara et al. 2017). The results suggest that SOCS3 suppresses a complete polarization to the M1 phenotype in these mice by blocking the IL-6 production.

In a different study using the same mouse line, the authors followed the timeline of inflammatory events in the brain. They demonstrated the presence of amyloid plaques and CD11b-positive microglia clusters in the hippocampus and neocortex at 4 months of age. Clustered glial fibrillary acidic protein (GFAP)-positive astrocytes were observed in the hippocampus and cortex after 6 months of age. Double staining with CD11b/GFAP antibody and thioflavin S showed clustered microglia and astrocytes that were in close association with amyloid plaques. TNF-α was detected at 8 months of age, while IL-1β, IL-6 and MCP-1 at 10 months. Double immunostaining indicated that TNF-α, IL-1β, IL-6, and MCP-1 were expressed by the activated microglia and a small part of activated astrocytes. These results demonstrate amyloid plaques and their associated inflammatory response developed at an early stage of life and progressively increased with age (Ruan et al. 2009).

A special role for the inflammasome has been proposed in the polarization of microglia to an inflammatory phenotype. Inflammasomes are multiprotein complexes that link pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) to the expression of certain pro-inflammatory cytokines. Inflammasomes contain a member of the NOD-like receptor (NLR) family, such as NLRP3 and IPAF, by which they are defined. The NLR protein recruits the inflammasome-adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), which binds to and activates caspase, promoting the processing of IL-1β and IL-18 (Lang et al. 2018). Stimulated by amyloid β (Aβ), the major component of amyloid plaques, NLRP3 assembles and activates microglia in the AD mouse model's brain, leading to the caspase-1 activation and IL-1β secretion. The activation of the NLRP3 inflammasome mediates microglia to exhibit inflammatory M1 phenotype (Zhang et al. 2020).

Microglial activation and its link to neurofibrillary tangles, and its major component, tau

Neurofibrillary tangles (NFTs) are a further histological hallmark of AD (Braak et al. 1986). NFTs are composed of the protein tau, a stabilizing component of the microtubular network, which participates in the transport of organelles including mitochondria, nutrients, and other cellular materials in neurons. In the AD brain, tau becomes hyperphosphorylated, and, as a result, the microtubule structure is compromised. This process leads to axonal degeneration and therefore disrupts the communication within the neuronal network (Ittner and Gotz 2011). Furthermore, tau is cross-linked through the oxidation and glycoxidation and forms insoluble deposits which occupy most of the internal intracellular space of an affected neuron (Ledesma et al. 1994; Thome et al. 1996a; Durany et al. 1999).

One study in AD patients at different stages has investigated the relationship of reactive glia with pathological hallmarks of AD to test whether glial cells are linked only to amyloid deposits or also to tangle deposition using a stereology-based approach. The authors observed that activated glia correlated positively with tangle burden but did not correlate with the amyloid load. They also suggest that reactive glia might contribute to the ongoing neurodegeneration, and tangle formation (Serrano-Pozo et al. 2011).

Transgenic mouse studies support the notion that microglial activation might drive tangle formation. For example, in P301S mice (a tauopathy mouse model), microglial activation and synapse loss precede the formation of tangles. Furthermore, the immunosuppression with FK506 (an immunosuppressant similar to cyclosporin) given already to young P301S mice slowed down the development of the tau pathology (Yoshiyama et al. 2007).

In a further mouse study in hTau mice (Maphis et al. 2015), multiple lines of evidence again suggest that microglial activation drives tau pathology. The authors show that microglial activation (CD45(+)) correlates with the spread of tau pathology in the hippocampus leading to spatial memory deficit. Finally, the application of an interleukin 1 receptor antagonist significantly reduces microglia-induced tau pathology (Maphis et al. 2015).

In terms of possible mechanisms, the pathways from activation of microglia to cytokine release and tau phosphorylation are suggested to involve the inflammasome as well as IL-1β. IL-1β is the key cytokine triggering tau phosphorylation in neurons (Ravichandran and Heneka 2021). Evidence for the participation of the inflammasome in this process includes the presence of an ASC and the pro-inflammatory cytokine IL-1β in microglia close to neurons containing hyperphosphorylated tau.

A further study suggests another, quite different mechanism linking microglia to tangle formation. Microglia isolated from the AD brain contained undigested tau particles, which the cells released into the extracellular space. The data suggest that microglia phagocytose aggregated neuronal tau, then fail to proteolytically digest it, and instead release tau seeds, which can then be taken up by previously unaffected neurons, thus spreading tangle formation to their neighbors (Hopp et al. 2018). Together, all these results suggest that reactive microglia are driving tau pathology and participate in the spread of pathological tau in the AD brain.

Further advances in microglial subtypes using next-generation sequencing methods

Using modern molecular biology methods and clustering, the number of microglia activation subtypes has expanded from the traditional M0, M1, M2a–c to around 7–8 different subtypes. For example, one study compared non-demented control and AD patients' post-mortem brain from the superior parietal lobe and the superior frontal gyrus, and investigated microglial transcriptomes at bulk and single-cell levels. In this study, seven different human microglial subpopulations based on their characteristic gene expression profile were identified. Interestingly, gene expression profiles and subcluster composition of microglia did not differ between AD patients and non-demented control subjects in bulk RNA sequencing nor in single-cell sequencing (Alsema et al. 2020). Another study, which used single-cell single-nucleus RNA-seq from microglia isolated from post-mortem tissue revealed eight microglia clusters. Clusters of microglia enriched for biological pathways identified clusters of interferon-stimulated microglia as well as a cluster of autophagic/phagocytic microglia (Prater et al. 2021).

In summary, M1-type microglia are abundant during AD progression, but appear to slow in the late stages of the disease. Furthermore, microglial activation is linked to both amyloid plaques and neurofibrillary tangles in both causal directions. For a more intensive insight into this area of research, the reader is pointed to these recent reviews (Jonas et al. 2022; Muzio et al. 2021; Knezevic and Mizrahi 2018).

The role of T cells (adaptive immunity) in AD

As outlined in the chapters before, the innate immune system is activated as the first line of defense, and if misdirected, can cause chronic (sterile) neuroinflammation as in the case of AD. In addition, lymphocytes of the adaptive immune system have evolved to provide a more versatile means of defense. The cells of the innate immune system, play a crucial part in the initiation and subsequent direction of adaptive immune responses. However, the involvement of the adaptive immune system in AD has been paid little attention until recently (Town et al. 2005). Interestingly, both CD4 positive and CD8 positive T cells have recently emerged as a possible contributor to the neuroinflammatory process in AD (Gate et al. 2020). In this very recent study, immune cell populations in the blood of patients with mild cognitive impairment (MCI) and AD were analysed, showing that these patients have increased levels of certain CD8 + cells (expressing CD45RA), termed T-effector memory cells. These T cells, terminally differentiated to effector memory cells re-expressing CD45RA (T-EMRA cells) (Gate et al. 2020). TEMRA cells have previously been linked to immunological memory, and they release inflammatory and cytotoxic (cell-death-promoting) molecules (Sallusto et al. 2004). This study found that the more circulating T-EMRA cells the demented subjects had, the worse they performed on cognitive tests. TCR sequencing of identified T-cell clones were found in two people with AD and one with MCI epitopes from the Epstein–Barr virus (Gate et al. 2020). While these results do not suggest that EBV causes AD, it contributes to the overall picture of infections and subsequent peripheral inflammation contributing to neuroinflammation and neurodegeneration. For a more depth insight into T-cell dysfunction in AD and other neurodegenerative disorders, the reader might take a look at the following

reviews (Dai and Shen 2021; Gonzalez and Pacheco 2014; He and Balling 2013).

The role of astroglia in AD

In addition to microglia, astroglial cells are also influenced by chronic neuroinflammation. They are transforming to a reactive state and may neglect their neuro supportive functions such as the production and supply of lactate to neurons, the uptake of glutamate, and the provision of glutathione precursors (Steele and Robinson 2012). In neuroenergetics, astroglia has emerged as the center stone in the concept of "lactate shuttles"; particularly the astrocyte-neuron lactate shuttle; pioneered by Magistretti and Pellerin (Magistretti and Pellerin 1996). The withdrawal of neurosupportive astroglial functions renders neurons vulnerable to neurotoxins including pro-inflammatory cytokines and reactive oxygen species ("neuroneglect hypothesis") (Fuller et al. 2010). Furthermore, human astroglia release NO, due to de novo synthesis of the iNOS following the cytokine exposure. NO regulates the release of pro-inflammatory molecules, interacts with ROS leading to the formation of reactive nitrogen species (RNS), and targets vital organelles such as mitochondria, ultimately causing cellular death (Heales et al. 1997). In summary, astroglia might turn from a friend to a foe in the context of chronic neuroinflammation, as suggested in these recommended reviews (Kumar et al. 2021; Valenza et al. 2021; Price et al. 2021).

The role of cytokines, free radicals, and reactive carbonyl compounds in AD

Increased levels of pro-inflammatory mediators such as TNF-α, IL-1β and IL-6, prostaglandins, and reactive oxygen and nitrogen species, are observed in the AD brain at all stages of the disease (Mrak and Griffin 2005). Among the cytokines, one of the most interesting cytokines concerning AD is IL-6. Huell et al. have shown that cortical senile plaques in AD patients display strong IL-6 immunoreactivity while no such immunoreactivity was found in the control brains (Bauer et al. 1991; Huell et al. 1995). In addition, high systemic IL-6 levels are also a predictor of dementia: (a) Elevated IL-6 in midlife predicts cognitive decline; the combined cross-sectional and longitudinal effects over the 10-year observation period corresponded to an age effect of 3.9 years (Singh-Manoux et al. 2014); (b) with data collected over 20 years from 2422 participants in the "Epidemiology of Hearing Loss Study", a greater likelihood of cognitive impairment in individuals with high or increasing IL-6 was observed (Wichmann et al. 2014). Guided by these suggestions, our group has characterised and validated a transgenic mouse model of IL-6 overexpressed in glial cells in the brain, created by Prof. Iain Campbell (Chiang et al. 1994).

Our group has examined inflammatory markers and neuronal degeneration as well as the motor performance of GFAP-IL6 mice at 3, 6, 14, and 24 months of age. Increased numbers of Iba1(+) microglia were observed as early as at 3 months of age. In addition, TNF-α levels proved to be significantly higher in the GFAP-IL6 compared to wild type (WT) mice at all time points. A difference in cerebellar volume between the GFAP-IL6 and WT mice was observed later in life, starting at 6 months and increasing to a loss of about 50% in 24 months old GFAP-IL6 mice. Synaptic deficits measured by postsynaptic density protein 95 (PSD95) levels decreased in the aging GFAP-IL6 mice from 14 months onward. Reduced performance on the accelerod beam walking test and higher ataxia scores were also observed (Gyengesi et al. 2019). These mice were used in curcumin rescue experiments, which will be detailed in a subsequent chapter.

In addition to cytokines and free radicals, macrophages and microglia also release toxic dicarbonyl compounds such as methylglyoxal (MGO). Our group has shown that MGO levels released from the activated RAW 264.7 macrophage cells increase about fivefold when cells are activated with 10 U/mL IFN-γ + 10 µg/mL LPS (Dhananjayan et al. 2017). Methylglyoxal (MGO) then forms advanced glycation endproducts (AGEs), which activate macrophages *via* the receptor RAGE, creating a vicious amplification cycle. The increase in MGO production can also be responsible for the increased formation of AGEs on plaques and tangles, contributing to crosslinking and insolubility, as already pointed out in the 1990s by Prof. Riederer's research (Münch et al. 1994a, 1997a; Thome et al. 1996a, 1996b; Loske et al. 2000).

Genome-wide association studies (GWAS) support the role of neuroinflammation in AD

Furthermore, early genome-wide association studies (GWAS) have identified three inflammation-relevant genes that are associated with AD: clusterin (CLU), complement receptor 1 (CR1) and triggering receptor expressed on myeloid cells 2 (TREM2) (Patel et al. 2014). The microglial receptor TREM2 plays a role in phagocytosis (e.g., in response to lipopolysaccharide on a bacterial invader) or microglial survival, and its link to AD is considered as one of the strongest supporting arguments for the role of neuroinflammation in AD. The list of immune-related genes and variants as risk factors for AD has now expanded

substantially, including not only CLU, TREM2, and CR1, but also CD33, APOE, API1, MS4A, ABCA7, BIN1, INPP5D, PICALM, and PLCG2. These genes are predominantly involved in pathogenic pattern identification, immune signaling, phagocytosis, phagolysosomal protein digestion. In summary of the more than 40 identified risk variants for AD, a majority of risk alleles are enriched in myeloid and microglia cells, suggesting a prominent role in microglial involvement in AD disease progression (Jonas et al. 2022).

What are the causes for microglia activation in AD?

In addition to dampening the microglial response by inhibiting intracellular pro-inflammatory pathways, a further option for anti-inflammatory AD pharmacotherapy would be the identification and blockade of the initial triggering factors. These possible triggers for microglial activation can include debris (intracellular components) from damaged and dying neurons (released also during acute during necrotic cells death induced by trauma, brain injury and stroke) including damage-associated molecular patterns "DAMPs", aggregates of pro-inflammatory and neurotoxic proteins, and pro-inflammatory cytokines as well as PAMPs, specific conserved bacterial and viral components(Mogensen 2009). DAMPs can be released from cells (including damaged and dying neurons) to alert the innate immune system and activate several signal transduction pathways through the interactions with the highly conserved pattern recognition receptors (PRRs) (Rosin and Okusa 2011; Clark and Vissel 2015).

DAMPs directly induce pro-inflammatory cascades and trigger the formation of the inflammasome, mediating the release of cytokines. DAMPs include Aβ, high-mobility group box 1 (HMGB1), the S100 family proteins, chromogranin A, and nucleic acids. Furthermore, Prof. Riederer's research has identified potent DAMP-like microglial activators, termed AGEs (Thome et al. 1996a). These protein modifications (particularly on lysine and arginine residues) are derived non-enzymatically from oxidized sugars and dicarbonyl compounds (Münch et al. 1998, 1999), and they bind to their receptor RAGE and lead to the activation of multiple inflammatory processes. 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 (Münch et al. 1997b, 1998).

In summary, all these findings suggest that the progression of many neurodegenerative diseases, including AD (Block et al. 2007), is at least partly driven by a cycle of self-perpetuating inflammatory neurotoxicity by the following mechanistic cascade: (a) Various inflammatory triggers can lead to the initial microglial activation. These triggers can be peripheral (e.g. systemic infections or peripheral chronic inflammation) or central (e.g. degenerating/dying neurons or amyloid deposits) (Gasic-Milenkovic et al. 2003) (b) These damaged or dying neurons release microglia activators, such as DAMPs (Wilkins et al. 2015), resulting in further microglial activation and thus maintaining the self-perpetuating cycle of neurotoxicity.

Based on these early studies, it is now generally accepted that affected regions of the AD brain are associated with activated microglia. With a host of inflammatory molecules, including complement proteins. Prof. Riederer and his group have been early adaptors of the "neuroinflammation hypothesis of AD" and "amyloid-only skeptics", when many others in the field put all their eggs in the "amyloid basket", and proposed that removal of β-amyloid by active and passive immunization would cure AD (Münch and Robinson 2002b; c).

In summary, Prof. Riederer was a pioneer recognizing the role of AGEs as triggering DAMPs in microglial activation (Münch et al. 1994b, 1998). Consequently, his group has already suggested targeting chronic neuroinflammation as a disease-modifying treatment (with antioxidants and AGE-inhibitors) for many neurodegenerative diseases including AD more than 20 years ago (Münch et al. 1998; Thome et al. 1996a; Durany et al. 1999).

Cytokine suppressive anti-inflammatory drugs (CSAIDs): a better alternative to conventional NSAIDs

The pharmacotherapy of peripheral inflammatory conditions is largely based on the use of non-steroidal anti-inflammatory drugs (NSAIDs). However, as NSAIDs are specific inhibitors of cyclooxygenases (COXs) which only decrease the production of prostaglandins but no other pro-inflammatory mediators, and thus they have limited anti-inflammatory action. In contrast, cytokine-suppressive anti-inflammatory drugs (CSAIDs) have a broader range of actions, they decrease the production of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, or NO produced by iNOS (Gunawardena et al. 2015, 2014). It was suggested that CSAIDs, drugs with a broader range of anti-inflammatory effects than the conventional NSAIDs may be effective to combat chronic neuroinflammation (Millington et al. 2014).

Natural compounds such as curcumin, apigenin, docosahexaenoic acid, epigallocatechin gallate, α-lipoic acid, and resveratrol have been identified to possess antioxidant, anti-inflammatory, neuroprotective, and cognition-enhancing effects. Among those, curcumin and apigenin

target the pro-inflammatory activator protein 1 (AP1) and nuclear factor kappa B (NF-κB) signaling pathways and inhibit the expression of many pro-inflammatory cytokines in the low μM range, and are therefore considered potent therapeutic CSAIDs (Guo et al. 2010; Strassburger et al. 2008; Sun et al. 2013). Both curcumin and apigenin exert a broad range of anti-inflammatory effects, they also penetrate the blood–brain barrier in animal models, and are safe (curcumin: generally regarded as safe (GRAS) by the Food and Drug Aadministration, apigenin: GRAS as the major ingredients of parsley and chamomile extract) (Millington et al. 2014).

Apigenin (4′,5,7-trihydroxyflavone) is a flavonoid found in chamomile, celery, grapefruit, and parsley (up to 0.5% wet weight in parsley: Apigenin inhibits IL-6, TNF-α and NO production in microglia at low micromolar concentrations (IC_{50} = approximately 4 μM) (Hansen et al. 2010b). Apigenin enters the brain, reaching a concentration of 1.2 μM after daily i.p. administration of 20 mg/kg apigenin for one week (Popovic et al. 2014). Furthermore, a variety of studies indicated CNS effects of apigenin when delivered i.p. or orally (Zhao et al. 2013). For example, apigenin (40 mg/kg) improved memory deficits in an amyloid-based transgenic mouse model of AD, the APP/PS1 mouse (Zhao et al. 2013). Apigenin reduces the numbers of $Iba1^+$ microglia by about 40–50% both in the cerebellum and hippocampus in GFAP-IL6 mice (Chesworth et al. 2021). Apigenin taken orally is systemically absorbed and recirculated by enterohepatic and local intestinal pathways. Studies about its bioavailability in humans have shown quite large values up to 30% (Meyer et al. 2006).

In our opinion, one of the most promising molecules to treat neuroinflammation and oxidative stress is curcumin, the principal curcuminoid of turmeric (*Curcuma longa*). A detailed overview of the nature of the molecule, metabolism, in vitro effects, and related mechanisms and effects in AD models as well as challenges with its bioavailability will be presentedin the next chapters.

Curcumin: a potent anti-inflammatory drug with bioavailability challenges

Curcuma longa is cultivated in tropical and subtropical regions, with most of the production coming out of India. The major compound in turmeric is curcumin, followed by demethoxycurcumin and bis-demethoxycurcumin. Its International Union of Pure and Applied Chemistry (IUPAC) name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Curcumin's overall structure consists of two aromatic ring systems containing phenolic groups, connected by a seven-carbon linker containing α,β-unsaturated β-diketone moieties. The yellow color of curcumin is caused by its absorption maximum of around 420 nm (Kunnumakkara et al. 2017; Jitoe-Masuda et al. 2013; Esatbeyoglu et al. 2012). In the mid-1990s, Professor Riederer already pointed out that the treatment of AD with antioxidants might counteract the oxidative stress seen in AD tissue (Retz et al. 1998; Rosler et al. 1998). At the same time, more and more evidence accumulated that the redox status of the cell is important for a variety of cell signaling pathways including those involved in inflammation. Many of those redox-sensitive signaling pathways lead to the activation of the transcription factors NF-κB and AP-1, well-characterized transcriptional regulatory factors that are induced by a wide variety of seemingly unrelated exogenous and endogenous agents. Changes in cellular oxidation/reduction status, communicated *via* a series of intracellular redox-sensitive signaling components employing metal- and thiol-containing proteins, serve as common mechanisms linking environmental stressors to redox-sensitive cellular responses. As such, these transcription factors are ideal paradigms to study the mechanism and possible physiological significance of early response genes in the cellular response to changes in cellular redox status (Gius et al. 1999; Mattson et al. 2004). Professor Riederer and his collaborators chose a variety of anti-inflammatory antioxidants and determined their ability to downregulate the production of NO in activated macrophages and microglia (Wong et al. 2001). These anti-inflammatory drugs are also termed CSAIDs. Furthermore, another mode of action of anti-inflammatory antioxidants might be the extracellular scavenging of hydrogen peroxide which acts as a second messenger in pro-inflammatory signaling between cells (Holmquist et al. 2007; Gunawardena et al. 2019).

Among the variety of anti-inflammatory antioxidants, curcumin has now taken a central role. It is an excellent scavenger of most ROS, including superoxide and hydrogen peroxide (Shalini and Srinivas 1987). Curcumin has a broad cytokine-suppressive anti-inflammatory action, downregulating the expression of COX-2, iNOS, TNF-α, IL-1, -2, -6, -8, and -12. It inhibits IL-6 mediated signaling *via* the inhibition of IL-6 induced STAT3 phosphorylation and consequent signal transducer and activator of transcription 3 (STAT3) nuclear translocation (Bharti et al. 2003), and interferes with the first signaling steps downstream of the IL-6 receptor in microglial activation (Ray and Lahiri 2009).

We have tested curcumin in a high-throughput screening system for anti-inflammatory and neuroprotective compounds, combining an "Enhanced Green Fluorescent protein" (EGFP) expressing neuronal cell line with N-11 microglia. Microglial activation leads to neuronal cell death, which can be conveniently measured by the loss of neuronal EGFP fluorescence. Moreover, we used this system to test selected polyphenolic compounds for their ability to downregulate inflammatory markers and to protect neurons

against microglial insult. Curcumin turned out to be one of the most potent compounds with the maximal neuronal survival at 10 µM (3.3 µg/mL) (Hansen et al. 2010a). In recent unpublished experiments, two doses of curcumin (20 µM and 50 µM) were investigated for their anti-inflammatory property of inhibiting NF-κB translocation (p65 subunit) in activated RAW 264.7 macrophages (LPS and IFN-γ) (10 µg/mL and 10 U/mL)] using the immunofluorescence microscopy (Fig. 1 and 2 in comparison to a "no curcumin" control. Cells pretreated with 20 and 50 µM curcumin (before being activated with LPS and IFN-γ) showed reduced nuclear p65 translocation (10.3% and 7.5%, respectively, compared to 100% translocation without curcumin). The 50 µM curcumin pretreated LPS and IFN-γ activated cells could limit the translocation to 7.5% (positive control). Again, this experiment suggests that therapeutic concentrations of curcumin lie in the micromolar range. When the potency of curcumin was determined with wide-range concentration–response experiments, our (yet unpublished) experiments suggest that curcumin concentrations at 16.7 ± 1.4 µM (approximately 6.14 µg/mL), 13.9 ± 2.1 µM (approximately 5.11 µg/mL), 23.6 ± 1.7 µM (approximately 8.6 µg/mL) are needed to suppress 50% of the inflammatory modulators (IC_{50}) of NO, IL-6 and TNF-α in 50 ng/mL of LPS and IFN-γ-induced murine macrophage RAW 264.7 cells. In phorbol 12-myristate 13-acetate (PMA)-differentiated human monocytic THP-1 cells, curcumin significantly inhibited LPS (1 µg/mL) induced IL-6 and TNF-α production with IC_{50} values of 5.8 ± 1.9 µM and 13.9 ± 2.1 µM, respectively (X. Zhou, submitted for publication). These data are consistent with other publications and indicate the therapeutic concentrations of curcumin need to be in the micromolar range, which is about tenfold higher than most tissue and plasma concentrations reported for even the most bioavailable oral formulations (Purpura et al. 2018; Kocher et al. 2016).

Curcumin as an anti-inflammatory and neuroprotective drug in animal models of AD

Animal research in transgenic models of AD has shown very promising results for curcumin in preventing the formation of amyloid plaques resulting in rescuing cognitive function

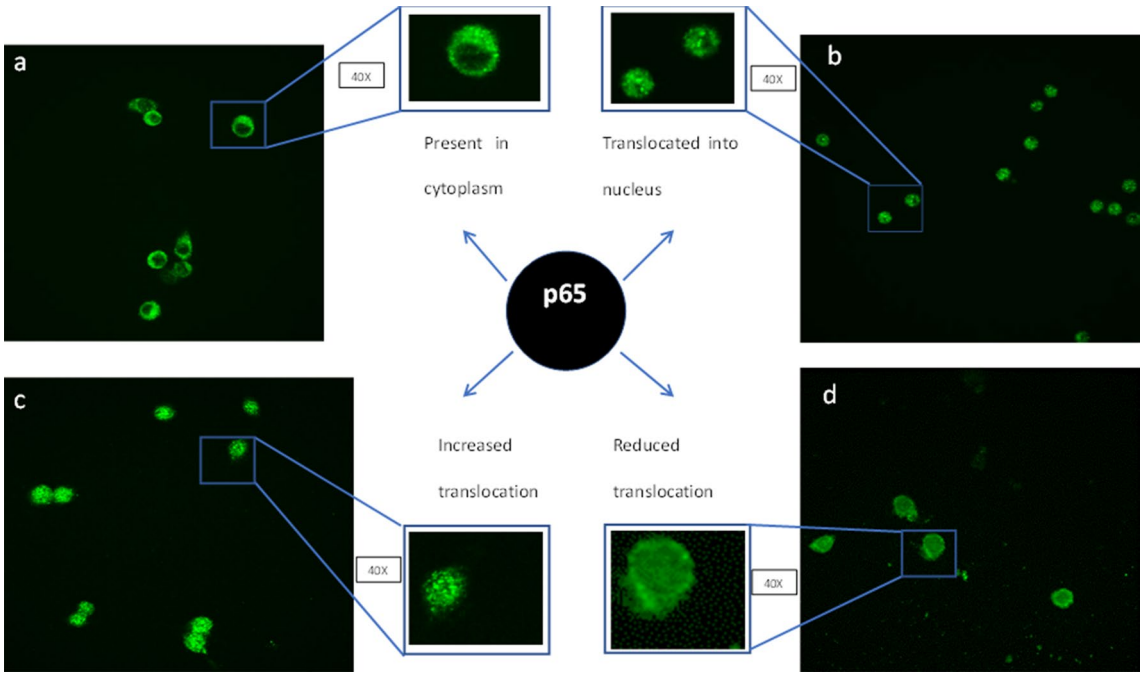

Fig. 1 Effect of curcumin treatment of cellular localization of NF-κB in RAW 264.7 macrophages. RAW 264.7 cells were treated with 0.1% fetal bovine serum in Dulbecco's Modified Eagle Medium media only (no activation) (p65 in the cytoplasm) (**a**), or activated with LPS and IFN-γ (10 µg/mL and 10U/mL) for 40 min (p65 translocated into the nucleus) (**b**). In **c**, **d**, pre-treatments with 20 µM and 50 µM curcumin for 1 h reduced the nuclear translocation of NF-κB induced by LPS and IFN-γ in RAW 264.7 macrophages (positive control). Fluorescence images were captured on a Zeiss AxioImager. M2 equipped with Apotome. Green Alexa Fluor 488 images (p65) were captured at the excitation wavelength of 491 nm and emission wavelength of 515 nm. Images were captured using the fluorescence intensity with an optimal signal-to-noise ratio. Image analysis was performed with a toolbox as modules with the free and open-source CellProfiler 14 software. The ratio of intensity in the nucleus in comparison to the cytoplasm was automatically, quantitatively, and objectively, of more than 100 pictures taken at 63X, high-throughput images. These are the representative images of three independent experiments performed

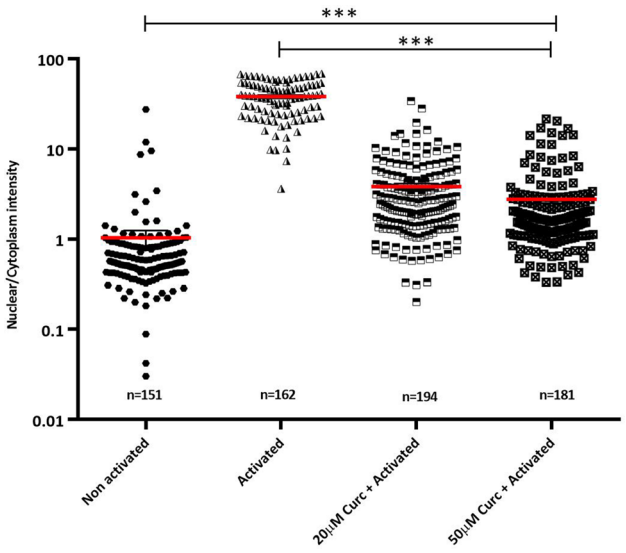

Fig. 2 Changes in nuclear: cytoplasmic fluorescence intensity ratios of NF-κB induced by LPS and IFN-γ in RAW 264.7 macrophages at different curcumin concentrations. Image analysis of multiple photomicrographs (see in Fig. 1) was performed with a toolbox as modules with the free and open-source CellProfiler 14 software. Curcumin was able to inhibit the translocation of NF-κB in LPS and IFN-γ activated RAW 264.7 macrophages by 89.7% (20 μM and 50 μM), respectively. Statistical significance was determined by one-way analysis of variance followed by Bonferroni's multiple comparison test using GraphPad Prism software version 7.03 (GraphPad Software Inc., La Jolla, CA, USA). Differences among different treatment groups and the LPS and IFN-γ stimulated group were significant at the values of $*p<0.05$, $**p<0.01$, $***p<0.001$, or $****p<0.0001$. Curc: curcumin.

to that of the wildtype (Sharman et al. 2019; Ringman et al. 2005). The mechanism behind curcumin's ability to inhibit plaque formation is its tight binding to β-amyloid. Using Synthetic Brain Membranes, curcumin was shown to reduce the number of nanoscopic $A\beta_{25-35}$ aggregate (Zou et al. 2021). In a similar study, curcumin molecules intercalate among the Aβ chains and bind tightly to them by hydrogen bonds, hydrophobic, π–π, and cation–π interactions. In the presence of CU, the Aβ peptides form a primary nucleus of a bigger size. The peptide chains in the nucleus become less flexible and more disordered, and the number of non-native contacts and hydrogen bonds between them decreases (Doytchinova et al. 2020).

A multitude of studies have investigated the effect of curcumin in transgenic amyloid-over expressing based models of AD and investigated curcumin's effect on plaque formation, a variety of different histochemical and biochemical markers and cognitive and behavioral deficits. In general, curcumin decreases amyloid plaque load, results in normalization of AD-specific biomarkers, as well in substantial improvements of behavioral deficits.

As this area of research is too exhaustive to be covered here in this review (which attempts to highlight and honor Prof. Riederer's scientific achievements in the field of cognitive and motor disorders), the reader is pointed to excellent reviews exclusively dedicated to the effects of curcumin in transgenic animal models of AD (Reddy et al. 2018; Ordonez-Gutierrez and Wandosell 2020; Pluta et al. 2022). Our group has also published a comprehensive review on this subject in 2022 (Ullah et al. 2022).

Cognitive effects of curcumin in human subjects

Contrary to the many animal studies, only a limited number of clinical studies have examined curcumin's effect on human cognitive functioning. The results of these studies are inconsistent; some studies report no cognitive-enhancing effects of curcumin (Baum et al. 2008; Ringman et al. 2012) whereas other studies suggest a beneficial effect of curcumin on cognition (Cox et al. 2015; Rainey-Smith et al. 2016; Small et al. 2018). The most important details of these human trials are summarized in Table 1. These inconsistencies in the human clinical trials may be related to differences in methodology and the included population.

However, we believe that the inconsistencies or failures in these human trials are simply because of suboptimal therapeutic concentrations of curcumin in plasma and brain of treated subjects. The pharmacokinetic reason behind the unsuccessful trials might be the extremely low bioavailability of oral curcumin, and the failure of the trial might simply have been caused by underdosing. Curcumin concentrations in the ng/mL range in plasma determined in comparative studies are orders of magnitude lower (Jager et al. 2014; Purpura et al. 2018), than the effective concentrations (or IC_{50}s) in cell culture studies.

Pharmacokinetic limitations of oral drug delivery of curcumin in human are due to extensive first-pass metabolism

Highly bioavailable curcumin formulations (encapsulated in liposomes or micelles) such as "Longvida" (VS Corp) or Meriva (Indena) can achieve μM concentrations in the animal brain (Begum et al. 2008; Ma et al. 2013). However, it appears that achievable doses in humans by oral application of curcumin are much lower. The mechanism behind it and the resulting suggestions for alternative application routes for curcumin other than oral will be outlined in the following sections. But this seems to be much more difficult to achieve in humans.

Table 1 Detailed information about the published clinical trials regarding the cognitive benefits of curcumin

Authors	Study population	Age	Doses and curcumin formulation	Duration (weeks)	Tests	Curcumin concentration in blood	Outcome
Baum 2008	36 subjects with progressive cognitive impairment	>50 years	Curcumin oral, 1 and 4 g/day or placebo	26	Mini Mental State Examination (MMSE)	Not detectable (free curcumin)	No benefit in the treated group
Ringman 2012	36 persons with mild-to-moderate AD	73.5 (avg) years	Curcumin C3 complex oral, 2 g/day or placebo	48	Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog)	7.3 ± 3.2 ng/mL (free curcumin) 96.0 ± 26.0 (total curcumin) (3 h after a 4 g dose)	No benefit in the treated group
Cox 2015	60 non-demented subjects	60–85 years	Longvida oral, 400 mg/day or placebo	Acute (1–3 h), Chronic (4 weeks)	Cognition: Computerized Mental Performance Assessment System (Northumbria University) Mood: Depression, Anxiety and Stress Scales (DASS21), Chalder Fatigue Scale (CFS)	Not determined	Working memory and mood were improved (chronic treatment)
Rainey-Smith 2016	160 non-demented subjects	40–90 years	Biocurcumax oral 1500 mg/day or placebo	52	A battery of clinical and cognitive tests incl MOCA and Cogstate	Not determined	Benefit in the treatment group in the MOCA, but not in any other test
Small 2018	40 non-demented subjects	51–84 years	Theracurmin oral 2 × 90 mg/day	78	Buschke Selective Reminding Test [SRT]) and visual (Brief Visual Memory Test Revised [BVMT-R]) memory, and attention (Trail Making A)	Not determined	Significant memory and attention benefits

One of the reasons why curcumin seems to be much more effective as a therapeutic in rodents than in humans is a difference in the degree of liver metabolism of curcumin and the resulting difference in bioavailability resulting in much higher free curcumin concentration in rodents than in humans due to the extensive first-pass metabolism of curcumin in the human liver (Sharma et al. 2007). In humans, oral curcumin is degraded at the alkaline pH in the intestine, it is also extensively metabolized by the gut microflora and the liver, leading to a substantial loss of free curcumin in the adsorption and metabolism steps (Ghiamati Yazdi et al. 2019). For example, free curcumin can be detected in rat plasma, whereas free curcumin is undetectable (or below 10 ng/ml) in humans except when the glucuronidation inhibitor piperine is taken concomitantly (Singh et al. 1986; Shoba et al. 1998).

Most orally ingested drugs are absorbed from the gastrointestinal (GI) tract and passed *via* the portal vein firstly through the liver, before being distributed into the systemic circulation. In the liver, many drugs are metabolized in a two-step process termed "first-pass metabolism" characterised by two different classes of chemical reactions, phase I and phase II (Sharma et al. 2007).

Phase I involves the cytochrome P450 enzymatic and consists of reduction, oxidation, or hydrolysis reactions. Phase reactions convert lipophilic and uncharged drugs into more polar or charged molecules by inserting or exposing a polar functional group such as $–NH_2$ or –OH. Phase II reactions are adding hydrophilic groups to the original molecule or the metabolite formed in phase I, and this further transformation is needed to increase its polarity. These phase II reactions include conjugation reactions, glucuronidation, acetylation, and sulfation. The ultimate goal of phase II reactions is to form water-soluble products that can be excreted by the body. Drugs that have already have –OH, $–NH_2$ or COOH groups can bypass Phase I and enter Phase II directly.

The metabolized compounds might still circulate in the body but if the pharmacodynamic properties have decreased (a decrease in the drug's potency), then the activity of the drug is deemed terminated. The pharmacokinetic result of first-pass metabolism means that only a certain proportion of the drug reaches the circulation in its active, unchanged form. Some of the pharmacokinetic studies mask the low levels of free curcumin by including glucuronidated and sulfated curcumin in their measurements, but because these compounds are much less active (Shoji et al. 2014), they would not contribute to the actual anti-inflammatory properties of curcumin in the metabolized state.

Curcumin also undergoes extensive reductive biotransformation in the liver. Curcumin's double bonds are subsequently reduced in enterocytes and hepatocytes by a reductase to dihydrocurcumin, tetra-hydrocurcumin, hexa-hydrocurcumin, and octa-hydro curcumin (Fig. 3). Phase II metabolism is quite active, in the intestinal and hepatic cytosol, on both curcumin and its phase I metabolites especially by conjugation with glucuronic acid and sulfate at the phenolic site. Curcumin is sulfated by sulfotransferases (SULTs) in the cytosol, mainly SULT1A1 and SULT1A3 (Fig. 4), whereas Uridine

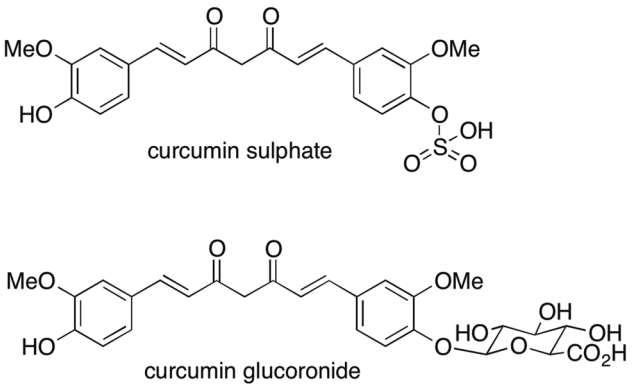

Fig. 4 Phase II metabolism of curcumin. Curcumin is sulfated by SULTs in the cytosol, and glucuronidated by UGTs in the intestinal and hepatic microsomes.

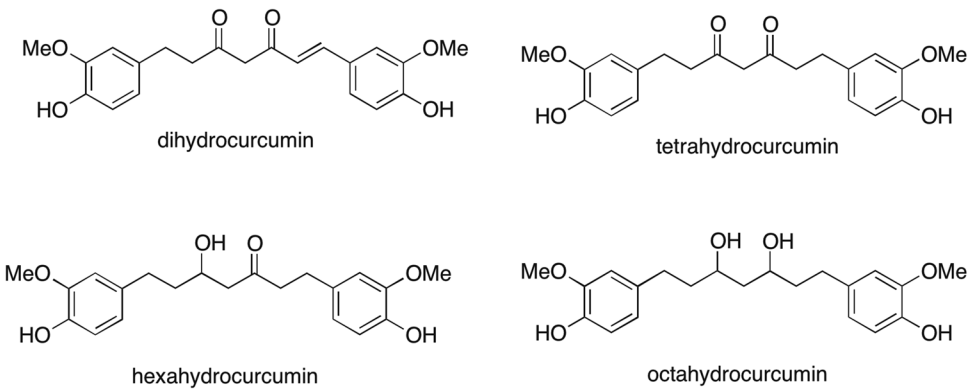

Fig. 3 Reductive biotransformation of curcumin. In the liver, curcumin's double bonds are reduced in enterocytes and hepatocytes by a reductase to form dihydrocurcumin, tetra-hydrocurcumin, hexa-hydrocurcumin, and octa-hydro curcumin

5′-diphospho-glucuronosyltransferase (UGTs) catalyze the glucuronidation of curcumin in the intestinal and hepatic microsomes (Fig. 4).

Alternative absorption routes for curcumin: a place for rectal delivery?

Therefore, we are suggesting exploring alternative ways for the delivery of curcumin, which avoids liver metabolism and boosts bioavailability. In general, injections or IV infusions, sublingual and transdermal formulations, inhalants, and rectal suppositories avoid the first-pass effect.

Among those, we propose that the rectum might be the most suitable delivery point for curcumin. The rectum is underused in many societies as a route for safe administration of drugs, most likely due to the intimacy or perceived uncleanliness of the site compared with more socially accepted non-invasive routes (de Boer et al. 1982). Rectal drug delivery offers unique pharmacokinetic properties due to its anatomical and physiological properties, which are different from the rest of the GI tract. The rectal region is drained by rectal (hemorrhoidal) veins and lymphatic vessels. The superior rectal vein drains into the portal vein, which passes the blood through the liver. However, the inferior and middle rectal veins drain into the inferior vena cava and thus directly into the systemic circulation bypassing the liver entirely. In summary, medications administered per rectum are ideal for local or systemic treatment, as the rectal mucosa has a blood and lymph supply that is capable of effective systemic absorption evading first-pass metabolism (de Boer et al. 1982). Among those, rectal application *via* suppositories or rectal capsules might be the safest and most effective way of delivery of curcumin. Suppositories are the most common rectally administered dosage form used clinically. Drugs that can be administered *via* a suppository include acetaminophen (for fever), diazepam (for seizures), and laxatives (for constipation) (Leppik and Patel 2015). However, despite these obvious pharmacokinetic advantages, the use of curcumin suppositories has been limited to only a few providers in the field. For example, Zetpil Nutritionals and Healing Bottoms offer curcumin suppositories. However, none of these providers has published pharmacokinetic data available in the peer-reviewed public domain.

Conclusion

In conclusion, Prof. Riederer's research into oxidative stress in PD and AD has led to the discovery of neuroinflammation as one of the major causes of free radical production in the brain. In AD, one of the most potent activators of microglia was identified as AGEs, sugar-derived protein modifications, which turn unreactive protein aggregates into potent pro-inflammatory activators, involving both microglia and astroglia. For the treatment of neuroinflammation, CSAIDs would be the most appropriate drug class. One of the best compounds in this drug class is curcumin, but its systematic absorption is too low to reach micromolar concentrations even with the best oral drug delivery systems. We suggest curcumin suppositories as the best alternatives as they allow to evade liver first-pass metabolism achieve high concentrations of curcumin in plasma and tissues, including the brain, opening a new pharmacological window into the brain for curcumin as a treatment for many neuro-inflammatory conditions including AD.

Acknowledgements Some of the experimental work was supported by a Ph.D. scholarship from the Western Sydney University (to M.V), and an ARC Linkage grant with Integria Healthcare (Grant number: LP160101594, to X. Z, G.M). X.Z. is supported by the Research Support Program Fellowship, Western Sydney University. No funding was received to assist with the preparation of this manuscript.

Author contributions All authors contributed to the study's conception and design. Material preparation, experiments, data collection, and analysis were performed by MV and XZ. The first draft of the manuscript was written by GWM (who was mentored by Prof. Riederer) and developed the idea of a historical review idea, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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