NOVEL CURCUMIN ANALOGUES AS INHIBITORS OF MICROGLIA PRO-INFLAMMATORY ACTIVATION IN RESPONSE TO AMYLOID-BETA OLIGOMERS

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Introduction: Increasing evidence posits that Alzheimer's disease (AD) pathogenesis and progression are not restricted to the neuronal compartment but involve many aspects, including neuroimmunology, and activated microglia, the brain-resident macrophages, play an important role in the disease progression. Misfolded and aggregated proteins, common pathological features of AD, bind to pattern recognition receptors on microglia and trigger an inflammatory response, which contributes to disease progression and severity. Being more easily manipulated targets than neurons, microglia are gaining increasing interest as a potential therapeutic or preventive strategy for the treatment of the inflammatory component of AD. Curcumin, a natural polyphenol, is emerging as a potential drug candidate due to its capability to affect multiple key pathways involved in AD, including neuroinflammation. Our aim was to identify novel curcumin-based analogues able to modulate Aβ-induced microglia activation, with the ultimate goal of developing novel pharmacological tools targeting neuroinflammation.

Material and methods: Two different populations of Aβ42oligomers namely monomers/dimers up to dodecamers (low molecular weight, LMW) and aggregates larger than dodecamers (high molecular weight, HMW) were prepared, analytically separated by capillary electrophoresis and isolated by ultrafiltration, to test their ability to stimulate an inflammatory response in primary microglial cells. To this end, microglial cells were first stimulated for 6, 24and 48h with increasing concentrations (5-20 μM) of Aβ42oligomers (LMW, HMW, or Aβ42in toto). Next, with the aim to improve the curcumin biological profile (i.e., efficacy, bioavailability, chemical stability, and toxicity), two analogues characterized by a prenyloxy moiety and a bromine atom on one aryl ring of the main scaffold (CUR6and CUR16, respectively) were designed and synthetized. To examine the anti-inflammatory profile of these compounds, microglia were exposed for 1h to analogues and then stimulated with Aβ42oligomers for 24h. Supernatants and cell lysates were collected and subjected to ELISA to measure the concentration of the pro-inflammatory cytokines TNF-α and IL-1β.

Results and conclusions: The release of TNF-α and IL-1β and the intracellular concentration of IL-1β were increased in response to stimulation with HMW oligomers and Aβ42in toto, starting from 24h. In contrast, LMW Aβ42oligomers failed to induce an inflammatory response in microglial cells. Finally, the release of TNF-α and IL-1β and the intracellular concentration of IL-1β induced by Aβ42oligomers were significantly suppressed by curcumin, CUR6, and CUR16treatment. These findings allowed us to develop novel curcumin analogues able to promote a microglia protective phenotype. This effect deserves attention to be further investigated and exploited in the search for novel and effective AD treatments.