Curcumin as a potential lead compound for the development of new anti-inflammatory agents useful to treat neurodegenerative diseases

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Neuroinflammation is a complex and multifactorial response of the central nervous system (CNS) to trauma, infection and neurodegenerative diseases, where cellular and molecular immune components such as specialized glial cells (microglia and astrocytes) are the main actors. In particular, microglia, the resident innate immune cells of the CNS, undergo rapid 'activation' in response to injurious stimuli, producing a plethora of inflammatory and potentially neurotoxic soluble factors, such as cytokines [*e.g.*, interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α], chemokines and reactive oxygen and nitrogen species (*e.g.*, nitric oxide). Although an efficient microglial immune response is necessary and critical for host defence, it is clear that over-activation of microglia contribute to neuronal cell damage in neurodegenerative diseases. Recent evidence suggests that microglia can be 'activated' in response to a systemic inflammatory stimulus. For example, a single peripheral injection of lipopolysaccharide (LPS), the major component of Gram-negative bacterial walls, in adult mice can lead to microglial activation and CNS inflammation that persists long after peripheral events have declined. Identification of molecules which prevent or down-regulate microglial inflammatory responses or direct microglia towards a protective anti-inflammatory phenotype could prove efficacious in neurodegenerative diseases in which inflammation is implicated. Recently, increasing interest has focused on identifying natural compounds with potential inhibitory effects on microglial activation and subsequent inflammatory processes. Among these compounds, curcumin (diferuloylmethane), the main bioactive component isolated from the rhizome of the turmeric plant (*Curcuma longa*) with multiple pharmacological effects, including anti-inflammatory activities, possesses neuroprotective properties against many neurodegenerative conditions.

This study investigated the effect of curcumin in an *in vivo* model of neuroinflammation based on a single systemic LPS injection. Adult mice were intraperitoneally injected with a single dose of 0.5 or 5 mg/kg LPS or vehicle and then tested for sickness behaviour (changes in body weight and food intake), mRNA expression (real-time PCR) of pro-inflammatory mediators (TNF-α, IL-1β, IL-6, cyclooxygenase- 2 (COX-2) and inducible nitric oxide synthase (iNOS)) and microglia activation (immunostaining with the microglial marker ionized calcium binding adaptor molecule 1) in different brain areas (frontal cortex, striatum, hippocampus and cerebellum). Both LPS doses induced a significant decrease in food intake and body weight within the first 48 h; however, only 5 mg/kg LPS significantly increased microglial activation and TNF-α, IL-1β, IL-6, COX-2 and iNOS gene expression. Furthermore, pre-treatment with curcumin (orally administered by gavage for 2 consecutive days before LPS injection) attenuated LPS-induced microglia activation and suppressed mRNA levels of TNF-α and IL-1β in all brain areas, while limiting expression of IL-6, COX-2 and iNOS to more selected brain areas.

These data show that curcumin can prevent neuroinflammation by modulating microglial activation and the expression of pro-inflammatory mediators *in vivo*, representing a promising lead compound to discover new drug candidates, with improved therapeutic efficacy in the treatment of neurodegenerative and age-related diseases with an inflammatory etiology.