



Inhalable Curcumin is an Efficacious Treatment Strategy for Herpes Simplex Virus Type 1-Induced Neuropathology

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Turmeric, which is derived from the root of the *Curcuma longa* plant, is one of the most widely used spices worldwide. Scientists from various disciplines have long studied the medicinal benefits of a polyphenol extract from *Curcuma longa*, curcumin. It has been shown to have a broad spectrum of pharmacological activities in cancer, inflammation, and Alzheimer's disease (AD) [1]. In an epidemiological study, continuous curcumin intake improved cognitive function in aged individuals [2]. Interestingly, curcumin inhibited the formation of amyloid- β fibrils in vitro as well as in vivo [3]. Furthermore, curcumin exhibits a variety of anti-microbial activities [1]. Curcumin has been shown to suppress herpes simplex virus type-1 (HSV-1) replication in Vero cells [4] by inhibiting the recruitment of RNA polymerase II to the promoter regions of HSV-1 immediate-early genes [5]. Despite its potential therapeutic efficacy, the clinical use of curcumin is restricted because of its poor aqueous solubility and relatively low penetration efficiency across the blood-brain barrier [6].

In a recent report, intranasal administration of the aerosolized curcumin derivative, FMeC1, efficiently targeted the frontotemporal cortex and hippocampus of 5XFAD transgenic mice with accelerated accumulation of amyloid- β [6]. FMeC1 was possibly transported from the nasal mucosa into specific regions of the brain via the olfactory conduit [7,8]. First, nerve terminals of olfactory receptor neurons are directly exposed to the external environment in the nasal cavity. Second, these neurons take up exogenous substances and use anterograde transport for trafficking into the limbic system. Third, the olfactory system is directly connected to the frontal cortex without thalamic relay. Intriguingly, similar to epithelial cells, but unlike other neurons, olfactory neurons undergo apoptosis and neurogenesis as part of a normal turnover process that continues throughout life [7]. Furthermore, neuronal stem cells in the subventricular zone of the adult brain predominantly migrate into the olfactory bulb, where they repair damaged olfactory neuronal circuits caused by toxic and infectious agents [8].

HSV-1 frequently uses the olfactory pathway to silently invade the human brain, where it targets the frontotemporal cortex and some limbic structures, such as the hippocampus [7,8]. It is conceivable that herpes simplex encephalitis (HSE) in children occurs during the course of primary HSV-1 infection, whereas in adults HSE arises from the reactivation of the latent virus in the brain [7,8]. It

should also be noted that the reactivation of HSV-1 in the brain is a potent risk factor for the development of AD [9]. Reactivated HSV-1 has been linked to an increased formation and accumulation of amyloid- β and abnormally phosphorylated tau. In addition, HSV-1-mediated disruption of autophagy in neurons also contributed to the accumulation of these abnormal proteins [10]. Additionally, upon HSV-1 reactivation, amyloid- β may be overproduced to exert its anti-HSV-1 activity, leading to amyloid plaque formation [11]. Thus anti-herpesviral action of curcumin is expected to limit the development of HSV-1-associated AD [12].

There is remarkable similarity in trafficking of inhaled curcumin and HSV-1 along the olfactory route. Therefore, I hypothesize that inhalable curcumin, in combination with standard anti-herpesviral drugs, will prevent and cure the HSV-1-induced neuropathology that is often associated with HSE and AD.

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