SHORT COMMUNICATION

Anti-neuroinflammatory effect of agaves and cantalasaponin-1 in a model of LPS-induced damage

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ABSTRACT
Chronic neuroinflammation is a key component of many neurodegenerative disorders. Chronic activation of this process produces pro-inflammatory cytokines, prostaglandins and reactive oxygen species that induce brain injury and neuronal dysfunction. Agave species contain saponins, compounds with anti-inflammatory activity. Extracts from A. tequilana (At), A. angustifolia (Aan), A. Americana (Aam) (125 mg/kg) and cantalasaponin-1 (5 and 10 mg/kg, isolated from Aam) were administered to male ICR mice with lipopolysaccharide (LPS)-induced neuroinflammation, after which inflammatory cytokines were measured in brain homogenates by using an enzyme-linked immunoassay (ELISA) test. All agave extracts and cantalasaponin-1, reduced brain concentration of LPS-induced pro-inflammatory cytokines IL-6 and TNF-α. Moreover, Cantalasaponin-1 increased the brain concentration of the anti-inflammatory cytokine IL-10. Agave extracts and derived compounds show promising results in the development of novel drugs for neuroinflammatory disease therapy.

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1. Introduction

Agave’s species have known anti-inflammatory effects, and are used to heal wounds, sores, traumas, fractures, rheumatoid arthritis, ‘psoriasis’ and viper bites (Monroy and Castillo 2007). Reports using animal models of inflammation have shown that extracts from *A. angustifolia* (*Aan*), have an anti-inflammatory effect against the oedema induced with 12-O-tetradecanoylphorbol-13-acetate (TPA) at 0.8 mg/ear (Hernández et al. 2014). The *A. americana* (*Aam*) hydrosolohoholic extract also induces anti-inflammatory activity in the carrageenan-induced oedema model (Misra et al. 2018). The acetonic extracts of *A. tequilana* (*At*), *Aam* and *Aan* as well as cantalasaponin-1 isolated from *Aam*, showed important anti-inflammatory activity, with a dose dependent inhibitory effect up to 90% at the highest dose of 1.5 mg/ear on a TPA-induced auricular oedema mice model (Monterrosas-Brisson et al. 2013). Extracts from *At* have also shown immunomodulatory effects in pristane-induced systemic lupus erythematosus (Gutiérrez-Nava et al. 2017).

No reports in the literature are available regarding the effect of Agave extracts in treating neuroinflammation, a self-defense mechanism that aims to reduce harmful stimuli and maintain brain integrity. Chronic neuroinflammation causes brain injury and neuronal dysfunction because of increased levels of inflammatory mediators, including reactive oxygen species, prostaglandins and cytokines (Salemme et al. 2016). The aim of neuroinflammatory disease therapy is to stop neurodegeneration, but current drug treatments are only able to slow down its progression, and carry side effects that affect the patient’s quality of life (Jellinger 2007), thus requiring the discovery of drugs that can accomplish better results.

The objective of this work was to evaluate the anti-inflammatory properties of extracts from *Aan*, *At*, *Aam* and of cantalasaponin-1 in a mice model of LPS-induced neuroinflammation (Zhang et al. 2018), in which the brain concentrations of different cytokines were measured by the ELISA method.

2. Results and discussion

2.1. Cytokines in the LPS-induced neuroinflammation

A well-known LPS-induced neuroinflammation mice model, consisting in the administration of intraperitoneal (i.p.) lipopolysaccharide (LPS) (Lee et al. 2008), was selected to evaluate the effect of *At*, *Aan* and *Am* extracts, as well as cantalasaponin-1 in the inflammatory cytokine profile of brain homogenates. All mice, except the BASAL group, received a daily dose of intraperitoneal (i.p.) LPS (0.25 μg/kg) for 7 days, after which they were administered the different treatments for 7 days, including agave extracts and cantalasaponin-1. The LPS-induced neuroinflammation was successfully achieved, with the VEH group showing the highest concentrations of pro-inflammatory cytokines IL-6, IL-1β and TNF-α, when compared to the group without damage (BASAL) and the one that received anti-inflammatory treatment with indomethacin (INDO) (Table S1).
In regard to the inflammatory modulation caused by agave extracts (Table S1), the At, Aan and Aam (125 mg/kg) extracts and INDO significantly reduced IL-6 and TNF-α levels when compared to the VEH group (*p < 0.05). Contrary to expectations, the concentration of IL-1β in the brain from animals treated with different Agaves, was similar or increased as compared to the VEH group. (*p < 0.05, Table S1). Although IL-1β is a pro-inflammatory cytokine, there are some reports that have shown that IL-1β alone is not harmful for brain tissue. Shaftel et al. (2007) have described a transgenic mouse model, IL-1βXAT, that utilizes the Cre/Lox system to initiate temporal and spatial expression of human IL-1β in the mouse brain. Mice showed no evidence of neuronal cell loss at two months post-IL-1β induction. This result may suggest that elevated IL-1β in a normal brain by itself is not harmful. Further studies should assess the role of increased IL-1β and if it is associated with a protective neurological effect.

Although saponins are known to modulate cytokine secretion (Li et al. 2018) and have anti-inflammatory properties like Akebia saponin D (Yu et al. 2012), panaxatriol saponins (Luo et al. 2011), Ginsenoside-Re, ginsenoside-Rd and ginsenoside Rg1 (Mohanan et al. 2018), no previous reports have addressed the anti-neuroinflammatory effect of cantalasaponin-1 or agave extracts. In this work we proceeded to evaluate cantalasaponin-1, a steroidal saponin isolated from Aam (Monterrosas-Brisson et al. 2013). Similarly Cantalasaponin-1 at 5 mg/Kg (CANTA 5.0) and 10 mg/kg (CANTA10.0) showed a significant reduction of TNF-α and IL-6 levels in comparison with the VEH group (Table S1). Different from what was observed with agave extracts, IL-1β values were also significantly reduced with CANTA 5.0 and CANTA 10.0 compared to the VEH group. Additionally, cantalasaponin-1 (CANTA 5.0 and CANTA 10.0 groups) was shown to increase brain levels of the anti-inflammatory cytokine IL-10, compared to VEH (*p < 0.05, Figure S1).

3. Conclusion

At, Aam and Aan extracts caused an immunomodulatory response on brain cytokines in a mice model of LPS-induced neuroinflammation, specifically reducing the levels of proinflammatory cytokines TNF-α and IL-6 and increasing IL-1β. The steroidal saponin, Cantalasaponin-1 isolated from Aam, at both concentrations evaluated, reduced IL1β, IL-6 and TNFα and also increased the levels of the IL-10 anti-inflammatory cytokine.

Disclosure statement

No potential conflict of interest was reported by the authors.

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