PubMed ▼

Format: Abstract

Full text links
ELSEVIER FULL-TEXT ARTICLE

J Ethnopharmacol. 2015 Aug 2;171:264-72. doi: 10.1016/j.jep.2015.05.058. Epub 2015 Jun 9.

Direct evidence for GABAergic activity of Withania somnifera on mammalian ionotropic GABAA and GABAρ receptors.

Candelario M[1], Cuellar E[1], Reyes-Ruiz JM[2], Darabedian N[3], Feimeng Z[3], Miledi R[2], Russo-Neustadt A[1], Limon A[4].

Author information

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Withania somnifera (WS) has been traditionally used in Ayurvedic medicine as a remedy for debility, stress, nervous exhaustion, insomnia, loss of memory, and to enhance cognitive function. This study provides an empirical evidence to support the traditional use of WS to aid in mental process engaging GABAergic signaling.

AIM OF THE STUDY: We evaluated the effect of aqueous WS root extract (aqWS), and its two main components, withaferin A and withanolide A, on the main inhibitory receptors in the central nervous system: ionotropic GABAA receptors.

MATERIALS AND METHODS: The pharmacological activity of aqWS, withaferin A and withanolide A, was tested on native rat brain GABAA channels microtransplanted into Xenopus oocytes and GABAρ1 receptors heterologously expressed in oocytes. The GABAergic activity of aqWS compounds was evaluated by the two-electrode voltage-clamp method and the fingerprint of the extract was done by LC-MS.

RESULTS: Concentration-dependent inward ion currents were elicited by aqWS in microtransplanted oocytes with an EC50 equivalent to 4.7 mg/mL and a Hill coefficient (nH) of 1.6. The GABAA receptor antagonist bicuculline blocked these currents. Our results show that aqWS activated inotropic GABAA channels but with lower efficacy compared to the endogenous agonist GABA. We also demonstrate for first time that aqWS is a potent agonist of GABAρ1 receptors. GABAρ1 receptors were 27 fold more sensitive to aqWS than GABAA receptors. Furthermore, aqWS activated GABAρ1 receptors eliciting maximum currents that were no significantly different to those produced by GABA (paired t-test; p=0.533). The differential activity on GABAA and GABA ρ1 receptors and the reported lack of significant GABA presence in WS root extract indicates that the GABAergic activity of aqWS is not mediated by GABA. WS main active components, witaferin A and withanolide A, were tested to determine if they were responsible for the activation of the GABA receptors. Neither compound activated GABAA nor GABAρ1 receptors, suggesting that other constituent/s in WS are responsible for GABAA receptor mediated responses.

CONCLUSIONS: Our results provide evidence indicating that key constituents in WS may have an important role in the development of pharmacological treatments for neurological disorders associated with GABAergic signaling dysfunction such as general anxiety disorders, sleep disturbances, muscle spasms, and seizures. In addition, the differential activation of GABA receptor subtypes elucidates a potential mechanism by which WS accomplishes its reported adaptogenic properties.

Copyright © 2015 Elsevier Ireland Ltd. All rights reserved.

KEYWORDS: Ashwagandha; Extrasynaptic receptors; GABA; GABAergic signaling; Synaptic receptors

PMID: 26068424 DOI: 10.1016/j.jep.2015.05.058

[Indexed for MEDLINE]