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Salvinorin A, an Herbal Secondary Metabolite from Salvia Divinorum as an Anti-Neuropathic Pain Scaffold

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Abstract

Salvia Divinorum (SD) is used since ages by the Mazatec shamans for initiation purposes. SD contains a number of diterpenes of which Salvinorin A (SA) is the most remarkable compound, and to date it is the strongest psychedelic plant compound we know of. It high selective affinity to the Kappa Opioid Receptor (KOR) system, and also influences the endocannabinoid, the dopaminergic and the serotoninergic neurotransmitter systems. Its traditional use by Mazatec healersis related to the treatment of gastrointestinal disorders, headache, rheumatism and to palliative care. Due to the pharmacokinetic properties with a very short half-life time, SA itself is not easy to use for clinical purposes. However, due to its unique pharmacology, the scaffold of SA might be of use in development special and new compounds for the treatment of neuropathic pain.

Keywords: KOR; Agonist; CB1; Endocannabinoid; Central

Introduction

Salvinorin A (methyl (2S,4aR,6aR,7R,9S,10aS,10bR)-9-acetyloxy-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxo-2,4a,5,6,7,8,9,10a-octahydro-1H-benzo[f]isochromene-7-carboxylate), is a strong psychedelic diterpene in SD, an ancient sacred plant for Mexican shamans, belonging to the family of the Lamiaceae. Since some decades dried leaves of the SD and its extracts have found its way into the global world as a psychoactive and legal food supplement [1]. The compound is identified as a new way to treat drug addiction [2]. Some isolated and rare cases of abuse of SA have induced legislation, and some countries started to criminalize SD, without clear or good reasons [3] Most people using SD do not transition to frequent or long-term use [4]. SD is mostly used most often to explore Altered States Of Consciousness (ASC) related to spiritual, mystical and transpersonal) experience [5]. SD is regarded as a sacred plant, is used in neo-shamanistic rituals, and it enables the user to enter the 'Salvia Space', resulting in valuable transpersonal insights. Earlier we discussed a comparable neo-shamanistic ritual using the Blue Nile Lilly extract and discussed the putative relevance of one of its compounds, nuciferine for psychiatry [6]. Salvinorin A might have a comparable use in medicine, both for a number of psychiatric disorders, such as substance dependency and abuse and depression [7,8]. Originally SD was and is used by Mazatec healers (practitioners known as a curandero, male or curandera, female) to cure diarrhea, headaches and rheumatism, and on the deathbed, as palliative treatment [9].

Brief Pharmacology of Salvinorin A

The psychoactive effects of Salvinorin A (SA) are quite psychedelic and much different from those induced by other psychoactive compounds, such as Cannabis, LSD, DMT etc. SA is a highly selective K-Opioid Receptor (KOR) agonist (Figure 1) [10]. The KOR a G protein-coupled receptor and is one of four related opioid receptors in the central nervous system that influence consciousness, motor control, mood and analgesia. SA also influences directly or indirectly the endocannabinoid system and dopaminergic systems and possibly the cholinergic system [11,12]. KOR receptor activation via Salvinorin A leads to the inhibition of dopamine turnover in the nucleus accumbens, leading to transient feelings of depression [13]. However, it has also dopaminergic activity on its own, independent of the KOR mechanism [14]. Most probably it has D2 agonistic properties [15]. Due to its KOR agonism, and its agonism for the cannabinoid CB1 receptor, SA received attention as a putative analgesic compound. We will present and discuss recent findings related to the anti-neuropathic pain characteristics of SA.

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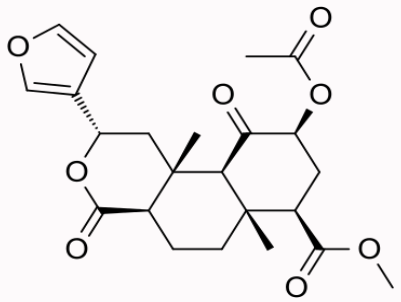

Figure 1: The diterpene Salvinorin A from Salvia divinorum: a non-opioid molecule with high affinity for the KOR receptor.

Salvinorin A in Neuropathic Pain

A search in Pubmed using keywords 'Salvinorin A' and 'pain' leads to the identification of 34 papers (PubMed search 10-12-18). SA is a remarkable molecule, the only natural diterpene compound with high affinity to the KOR system, with additional affinity for the CB1 receptor [16]. These special pharmacological properties have raised interest in the scaffold of SA as a template for new anti-neuropathic compounds. A number of studies pointed out that SA has analgesic properties in various models [17-21].

Guida et al. [17] described the effect of SA on spinal cord level, where it reduced the neuronal hyperexcitability [17]. They also found an additional mechanism of action on the level of glia: SA reduces glia hyperactivation, comparable to the effects of the anti-inflammatory and analgesic autacoid palmitoylethanolamide.

Certain modifications of SA have already been tested in animal models of pain, including visceral pain, and had a longer duration of action compared to the mother compound SA [22,23].

A recent study specifically focused on neuropathic pain as an indication for SA or its derivatives, supportive for a central mechanism leading to the reduction of neuropathic pain. Coffeen et al. [23] tested the effects of SA administration directly in the Insular Cortex (IC) during chronic nociception through a neuropathic pain model [24]. Given the absence of clarity whether the analgesic activity of SD is induced via the KOR of the CB1 receptor, they also wanted to check whether the analgesia was mediated by the opioid or cannabinoid system via KOR or CB1 receptors, respectively. The pain test system was the sciatic nerve ligature (SNL) model in a hind paw. Twelve days after ligature, a cannula was inserted stereotaxically positioned on the left rostral agranular insular cortex (RAIC). In the SA group of 8 rats, the basal values obtained by plantar and mechanical nociception were assessed prior the sciatic ligature. 12 days after the nerve ligature, both tests were performed immediately and 1 h after microinjection of SA (11.55 nm/ lL, 2 lL/min). The same procedure with SA, while also adding a KOR antagonist (nor-binaltorphimine dihydrochloride, NOR-BNI), or a CB 1antagonist (AM-251). The results were a decrease in both mechanical and thermos-nociceptive response, immediately and 30 min after the administration of SA in the IC. The analgesic effect could be totally blocked by the co-administration of NOR-BNI and AM251 (the KOR and CB1 antagonists), and by administration of each antagonist separately, the blockade was less intense. Previously it was found that SA does not directly activate the CB1 receptor and Coffeen et al. [23] found that the anti-nociceptive effect of SA could be reversed with AM251. As a possible mechanism, the authors suggested crosstalk between KOR and CB1 receptors or the formation of heterodimers between these two different receptors. Due to the fact that oral administration of SA is not the most optimal way, the authors suggested an intranasal administration of a special formulation, leading to a swift access to the drug to the brain and they stated that currently, a multitude of such dosing devices are in development. They further suggested a delivery of SA by inhalation. Such new formulations might be of great use to treat neuropathic pain patients, as the onset of action is expected to be fast. Key for such development will be a correct dose-finding study, to avoid inducing the psychoactive effects of SA.

Conclusion

SA has an anti-inflammatory and analgesic profile, in addition to its profile as an anti-craving compound. In a neuropathic pain model, centrally applied SA could inhibit pain. The analgesic activity could be partly reduced by a KOR antagonist and a CB 1 antagonist. Application of both antagonists led to a complete abolishment of analgesia. New formulations of SA, making use of the intranasal way or by inhalation will be required to optimally develop SA as an analgesic therapy. Dose-findings studies will be quite important to find the lowest effective dose and avoid the psychoactive side-effects. The SA scaffold is unique and is currently used to develop new chemical entities for a number of indications.

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