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Review

Sparteine as an anticonvulsant drug: Evidence and possible mechanism of action

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ABSTRACT

Sparteine is a quinolizidine alkaloid extracted from *Lupinus* that has numerous pharmacological properties both in humans and animal models. In the central nervous system, sparteine reduces locomotor activity, has light analgesic effects, also has no effects on short-term memory or spatial learning and does not induce changes in behavior or electroencephalographic (EEG) activity. However, the anticonvulsant profile of sparteine is not fully characterized in experimental animals and there are no data in humans. Therefore, the present review focuses on the experimental evidence supporting the anticonvulsant action of sparteine in models of acute seizures and *status epilepticus* (SE), as well as its possible mechanisms of action. The evidence that supports the anticonvulsant effect of (−)-Sparteine sulfate includes the inhibition of seizures induced by maximal electro-stimulation, a delay in the onset of convulsive behavior and the prolongation of survival time in mice treated with pentylenetetrazole (PTZ). Additionally, sparteine delays the onset of convulsive behavior and decreases the severity and mortality of rats treated with PTZ and pilocarpine. Sparteine decreases amplitude and frequency or blocks the epileptiform activity induced by PTZ, pilocarpine and kainic acid. Sparteine may decrease hyperexcitability through the activation of the M2 and M4 subtypes of mAChRs, which is a probable mechanism of action that together with its systemic effects may favor its anticonvulsant effects against seizures and SE.

1. Introduction

Many compounds derived from herbs have been used in medicine to treat seizures and epilepsy, and the identification of the active constituents has demonstrated that alkaloids, flavonoids, terpenoids, saponins and coumarins exhibit anticonvulsant activities [1]. The species of *Lupinus* have been used for centuries across large geographic areas and have important uses in food and medicine for both animals and humans [2,3]. *Lupinus* seeds have high protein, oil, fiber and carbohydrate contents, but most importantly, these seeds are high in alkaloids (approximately 1%) [4,5]. Four hundred species of *Lupinus* have been reported across the world [6]. Inter- and intra-species variations in quinolizidine alkaloid contents have been reported; however, more than 100 quinolizidine alkaloids have been reported in wild species of *Lupinus* [7,8]. Sparteine and lupanine are the most abundant quinolizidine alkaloids in wild *Lupin* species [9]. Additionally, sparteine is available as a commercial product that is also known as lupinidine ((−)-Sparteine, Sigma–Aldrich, St. Louis, MO, USA).

2. Sparteine

Sparteine is a quinolizidine alkaloid and was first extracted from Cytisus scoparius, but it can also be isolated from several *Fabaceae* species, including *Lupinus*, *Spartium*, and *Cytisus* [10,11]. The content of sparteine depends on the variety, habitat, phenology, plant organ and weather conditions [12–15]. Sparteine has been found in both old and new world *Lupinus* species [16].

2.1. Chemical structure and properties

Sparteine is a heterobicyclononane alkaloid [17,18] with 4 asymmetric carbon atoms that should exist in several stereoisomeric forms [19]; the chemical and physical properties of

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sparteine depend on its presentation (Table 1). Specifically, sparteine sulfate has good physical properties that allow for its use in the clinic and in experimental animals. Sparteine, (−)-Sparteine sulfate and (+)-Sparteine can be dissolved in water, which makes these compounds suitable for oral administration. Moreover, the predicted data generated using the ACD/Labs Percepta Platform enable predictions about the abilities of sparteine to be absorbed, to successfully reach the intended target, and to be metabolized and excreted (Table 1).

2.2. Pharmacology of sparteine

Sparteine has demonstrated numerous pharmacological properties both in humans and animal models. For example in the cardiovascular system, sparteine has been found to exhibit antiarrhythmic activity (it is a class 1a anti-arrhythmic agent), to reduce the incidences of ventricular tachycardia and fibrillation, and to reduce heart rate and blood pressure [11,20–31]. In the pancreas, sparteine induces insulin and glucagon secretion and exhibits a hypoglycemic effect [31–37]. Sparteine has also demonstrated protective activity against diabetes-associated DNA damage [38]. Additionally, sparteine has been used to induce uterine contractions and has been demonstrated to exhibit diuretic and anti-inflammatory activities [39,40]. Sparteine has been found to exhibit bactericide-like activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Bacillus thuringienis* [41].

The pharmacological proprieties of sparteine in the cardiovascular system and its hypoglycemic effects have been widely studied. In this respect, sparteine has been demonstrated to exhibit Na^+ and K^+ channel-blocking effects, and these properties favor its antiarrhythmic action against electrical and ischemic arrhythmias via concentration-dependent reductions in Na^+ currents, hyperpolarization due to Na^+ channel inactivation, and elevation of the rate of decay of the transient outward K^+ current [26,30]. However, the anticonvulsant effect on seizures and the inhibition of non-convulsive seizures have not been well studied and described.

Toxicological studies in experimental models with sparteine ((−)-Sparteine sulfate, Sigma–Aldrich, St. Louis, MO, USA) have reported that the maximal non-lethal doses (LD0) of sparteine in mice range from 25 to 30.7 mg/kg intraperitoneally (i.p.) [42,43] and 75 mg/kg subcutaneously (s.c.) [44]. In rats, on postnatal days 1–3, the LD0 is 25 mg/kg s.c. [45]. Sparteine has no toxic effects at 40 or 80 mg/kg in the liver, heart or kidneys as demonstrated by observations of normal morphological patterns in female and male rats [9]. The LD0s in rabbits range from 100 to 120 mg/kg s.c. and 30 mg/kg intravenously (i.v.) [44,46]. Others studies have reported the lethal dose of sparteine in 50% of exposed animals (LD50) ranges from 36 to 67 mg/kg i.p. [42,47] and 220 mg/kg orally [42]. In adult rats, 160 mg/kg administered orally causes weight loss and mortality in 40% of the animals and decreases in blood glucose levels [9]. Lethality in 100% of animals (LD100) due to sparteine occurs at 100 to 150 mg/kg i.p. in mice [43,48] and at 500 mg/kg following oral administration [19], whereas in rats at postnatal days 1–3, the LD100 has been reported to be 3050 mg/kg s.c. [45], and the LD100s range from 45 to 50 mg/kg i.p., 75 to 110 mg/kg s.c. and 50 mg/kg i.v. in adult rats. The LD100s in rabbits are 500 mg/kg orally and 100 mg/kg intramuscularly (i.m.). Additionally, the LD100s in guinea pigs are 42–44 mg/kg i.p., 66 mg/kg i.m. and 92–95 mg/kg s.c. [19].

There are limited data regarding the toxic dosage of sparteine in humans; however, in moderately overweight individuals, doses of 240 mg (i.v.) of sparteine sulfate do not result in any apparent acute toxicity, and the therapeutic dose of sparteine sulfate for the induction of a hypoglycemic effect ranges from 75 to 600 mg/day [33,49]. The administration of 200 mg i.v. does not produce collateral effects in the brains or spinal cords of patients; however the administration of 300 mg i.v. produces slight dizziness, palpitations, and tingling of the hands and fingers, the skin becomes moist, and respiration may be profuse. No toxic effects on fetuses have been noted [19].

The metabolic activation of sparteine in the liver produces highly reactive molecules that are capable of reacting with macromolecules such as DNA [50]. However, a comet assay in staminal nuclei of *Tradescantia* demonstrated that sparteine sulfate exhibits genotoxic activity at 0.5 mM (but not at 0.01, 0.1 or 1.0 mM doses). The authors of this study concluded that the comet assay used to study the genotoxicity of sparteine sulfate [51] is desirable only to study very low concentrations of compound.

2.3. Effects of sparteine in the central nervous system

Sparteine inhibits transmission from the sympathetic ganglia to the autonomic nervous system [23,48,52]. Based on this ganglionic property, sparteine is an antagonist of the ganglionic $\alpha 3\beta 4$ nicotinic receptors [53,54]. At high doses, sparteine can reduce the reflection of the carotid sinus, the coronary flow, contraction, and extent and the heart rate [55,56], but sparteine can also reduce locomotor activity and possesses slight analgesic and sedative effects [43].

Garzón-de la Mora and coworkers [9] demonstrated that sparteine sulfate treatment for seven consecutive days has no effect on short-term memory or spatial learning in female or male rats when administered at 40, 80 and 160 mg/kg through oral cannulae. Additionally, sparteine (13 mg/kg, i.p.) does not induce behavioral changes, and the electroencephalographic (EEG) activities of animals treated with this concentration of sparteine are characterized by slow, low-amplitude and – frequency activity compared with control animals treated with saline solution [57].

2.4. Experimental evidence regarding the anticonvulsant action of sparteine

There is little evidence about the anticonvulsant effect of sparteine. The models that have been used to test the anticonvulsant effect of sparteine have involved models of acute seizures or status epilepticus (SE). SE is a pathological condition in which the patient requires urgent hospitalization and emergency treatment. SE is associated with substantial morbidity and mortality [58,59]. SE has an incidence of up to 61 per 100,000 people per year and is divided into four sequential stages (early, established, refractory and super refractory) that are important in the pharmacotherapy of SE [60]. Recently, the following new definition of SE was proposed: a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures (after 5 min). SE is a condition that can have long-term consequences (after 30 min), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of the seizure [60].

In female and male Wistar rats treated with 40 mg/kg of sparteine through a metallic cannula during seven consecutive days, the sparteine produced 100% inhibition of seizures induced by a maximal electro-stimulation (METsc) on the 8th day compared with 65% and 55% inhibition rates in male and female rats, respectively, that were treated with 30 mg/kg of carbamazepine [9]. Additionally, mice treated with sparteine (13 mg/kg, i.p.) 30 min before pentylenetetrazole (125 mg/kg, i.p.) exhibited a delay in the onset of first seizure and prolonged survival time [43]. Most recently, a study of Wistar rats provided support for the anticonvulsant effect of sparteine [57]. In this work, sparteine (13 mg/kg, i.p.) was injected into the animals 30 min before pentylenetetrazole, pilocarpine or kainic acid injection, and