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Salvinorin A for Stroke Rescue Purposes

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Abstract

In this perspective, I summarize the current evidence that salvinorin A could be used for stroke rescue. A recent study to demonstrate the effectiveness of intranasal salvinorin A to improve long term neurological outcome in a monkey ischemic stroke model is very promising. Current accumulated evidence indicates that salvinorin A can improve stroke outcome through various mechanisms. While salvinorin A has side effects of diuresis, hypothermia, reduced brain metabolism, and psychotropic effects, these could potentially all contribute to protective effects in the setting of stroke.

Keywords

Salvinorin A, Stroke, Mechanism, Ischemia, Hemorrhagic, Outcome

Introduction

Salvinorin A (SA) is a small molecule (432.4 g/mol) that is the main active component readily isolated from the plant salvia divinorum [1]. It has been ingested for centuries for religious ritual and recreational purposes [2]. SA is a kappa opioid receptor (KOR) agonist that isthe most potent KOR agonist from a natural source known to date. It displays no respiratory depression, and there is limited or no addiction potential [3] reported so far despite decades of human usage. It is unique in that it is a non-opioid molecule structurally unrelated to any other known opioid agonists. It is a hydrophobic molecule that rapidly enters the brainand that can reach peak concentration within seconds [4,5]. We have discussed its potential usage for stroke therapy [6]. A recent landmark study demonstrated the effectiveness of SA in improving long term neurological outcome (28 days after stroke) in a monkey stroke model [7]. The critical importance of this study is that it used a monkey model with autologous blood clot to closely simulate the common clinical stroke scenario. The decrease of the infarct size and improvement in long term neurological outcome is encouraging and convincing, despite being a small scale preliminary trial. This study used an intranasal SA administration strategy for potential acute rescue purposes. An intranasal formulation allows for easy and rapid delivery of SA in emergent and pre-hospital settings. This route also avoids the hepatic first-pass metabolism [8] and direct hydrolysis of SA from intravenous administration. In addition, intranasal administration of appropriately formulated drugs can directly access the brain by bypassing the blood brain barrier and reducing off-target effects [9]. It is important to point out also that other potential neuroprotective agents are generally administered intravenously. In a stroke, the problem is lack of blood flow to a region of the brain, therefore an intravenous therapy would be severely limited in its access to the part of the brain that needs protection the most. An intranasal approach with a small hydrophobic molecule like SA can access all areas of the brain by simple diffusion.

The Evidence of Protective Effects in Various Preclinical Models

The first study of SA on the brain neurovascular unit started with the discovery that SA can selectively dilate brain vessels via the KOR receptor and K_{ATP} channels and nitric oxide pathway in a piglet model [10]. Subsequently, it was discovered that SA can preserve cerebral vascular autoregulation in a piglet model of hypoxia/ischemia whether it is given prior to ischemia or after reperfusion [11,12]. SA reduces neonatal mortality and improves neurological outcome in a rodent neonatal hypoxia model. Intranasal SA improves neurological outcome in a rodent middle cerebral artery occlusion (MCAO) model [13]. One of the major concerns with any potential stroke rescue therapeutic is whether a drug like SA with known cerebral vasodilatation properties [10] would be contraindicated in hemorrhagic stroke, or if it could cause or exacerbate hemorrhagic transformation of an ischemic stroke. Hemorrhagic transformation, hemorrhagic infarction and parenchymal hematoma, following ischemic stroke is a significant concern, being the result of multiple co-existing factors both systemic and cerebral [14]. Major contributors to hemorrhagic transformation of ischemic stroke are the size of the infarct and reduction of collateral perfusion of the surrounding penumbra [15] and loss of cerebral blood flow autoregulation [16]. SA has been shown to reduce ischemic infarct size [7,13], and along with its vasodilatory properties [10] and protection of cerebral autoregulation [11]

would be expected to potentially reduce the possibility of hemorrhagic transformation of ischemic stroke. Current evidence also indicates that SA has robust efficacy in a model of hemorrhagic stroke, the mouse subarachnoid hemorrhage model [17]. Efficacy, or at a minimum no additional harm, in hemorrhagic stroke is of critical importance to any new acute stroke therapeutic. Current treatment, specifically tPA requires a neuroimaging study be performed prior to administration, since clot dissolution would definitely be contraindicated in hemorrhagic stroke. A drug that would benefit hemorrhagic stroke, or at least not exacerbate it, would save precious time by being able to be administered immediately after recognition of stroke, and prior to precious time-consuming definitive hospital based neurodiagnostic confirmation of the type of stroke. Neuroprotective effects of other KOR agonists besides SA have been demonstrated in brain hypoxia and ischemia models in a variety of different animal species [18], but so far none, other than SA, have demonstrated significant clinical value due to their intrinsic opioid characteristics, low selectivity, or lack of clinical safety profiles [19]. Many attempts at developing acute stroke therapeutics have been tried and ultimately failed to deliver on clinically significant neuroprotection. KOR agonists, specifically SA, are fundamentally different in action from that of many other potential therapeutics based on specific targets such as those posited by the 'excitotoxicity' model of stroke [20,21]. KOR agonists, especially SA, need to be developed further and advanced to clinical trials as soon as possible.

Mechanism of Actions

It is clear that the key mechanism of SA protective effects is through KOR activation. Use of a KOR antagonist can abolish the protective effects and the brain vascular dilatation effects of SA [10,13]. Based on a recently published study using a cell culture hypoxia model, it appears that SA may be working through the beta-arrestin pathway rather than through the G protein pathway [22]. KORs are widely expressed throughout the brain. Evidence that KORs redistribute during ischemia [13,23], and data on the phenomenon of pre- and post-conditioning of ischemic stress [24] indicate that opioid receptors are functionally part of a natural defensive response to a sudden lack of blood flow [23]. This idea is borne out by the pleiotropic nature of the effects of SA in cerebral ischemia studies. SA has been shown to possess selective cerebral vessel dilatation properties [10], anti-inflammatory properties [17,25], cerebral auto-regulation protection [11], immuno-modulation properties [26], and diuretic effects [19]. Of major significance is that SA has been shown to protect the blood brain barrier in ischemia [13]. Another potentially important effect of KOR agonists, including SA, is hypothermia [27,28]. KOR mediated hypothermia has been shown to reduce metabolic demand during caloric restriction [29]. Cerebral hypothermia may play a role in neuroprotection, as it has been reported that hippocampal damage is almost completely abolished in rats by a reduction of only 2-3 °C in the brain during ischemia [30,31]. It is also possible that SA could offer protective effects through immune-modulation, based on a recent study on pulmonary macrophages and the inflammation process [32,33]. Table 1 summarizes the multiple potential mechanisms and evidence that SA could offer an exciting new therapeutic option in the setting of acute stroke rescue based on the current available experimental data.

Table 1: Why Salvinorin A is suitable for stroke therapy.

Selective brain vessel dilatation	[10]
Anti-inflammatory properties	[17,25]
Cerebral auto-regulation protection	[11]
Immuno-modulation	[26]
Protects blood brain barrier	[13]
Diuretic effects	[19]
Small molecule	[37]
Passes through blood brain barrier	[4]
Easy administration (intranasal etc.)	[38]
Quick onset (within seconds)	[39]
High potency (nM)	[37]
Hypothermic effects	[40]
Decrease brain metabolism	[5]
Acts on specific receptor	[41]
History of long-term human use	[2]
From natural source	[1]
Mouse stroke model efficacy	[13]
Pig hypoxia model efficacy	[10-12,42]
Monkey stroke model efficacy	[7]
Brain ischemia model efficacy	[13]
Subarachnoid hemorrhage efficacy	[17]

An example of our ongoing efforts to study potential direct neuronal protective effects of SA is shown in Figure 1 (unpublished data). For this study rat primary culture cortical neurons were exposed to oxygen and glucose deprivation to ascertain whether SA has can preserve cellular structural features observed under electron microscopy. As indicated in the figure, our preliminary results indicate that subcellular structure appears to be protected in rat primary cortical neuronal cells exposed to SA during 4 hours of oxygen glucose deprivation (OGD).

Psychotropic Effect of SA

SA has been reported to have rapid and short-lived euphoric hallucinogenic activity, rather than the dysphoric effects seen in classic KOR agonists [34]. In hu-

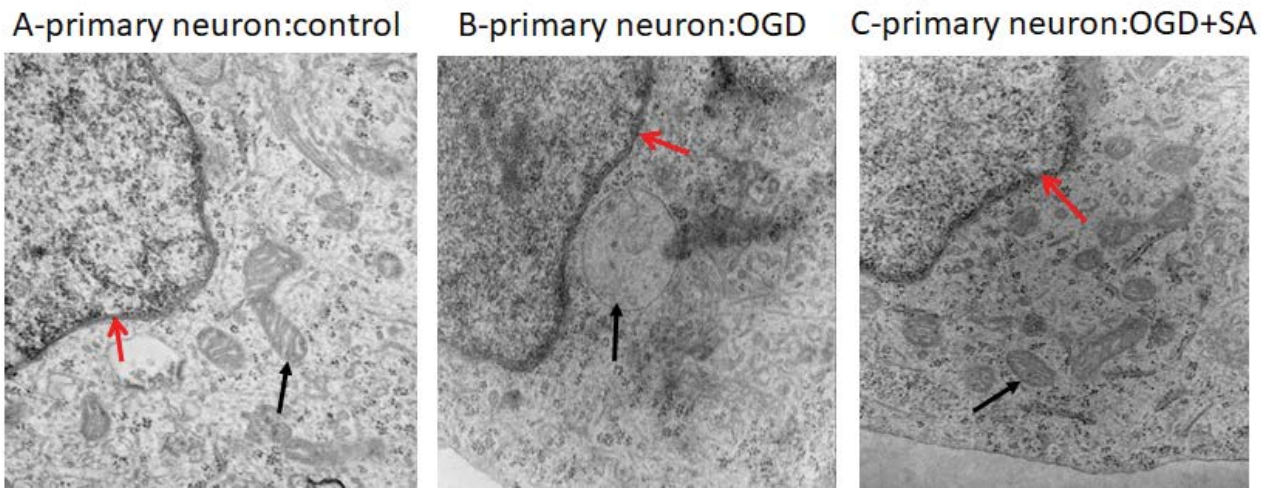

Figure 1: Subcellular changes in the rat primary cortical neuron. (A) Nuclear (red arrow) and well-structured mitochondria (black arrow) are seen in control; (B) Swollen mitochondria are observed in OGD exposed cortical neurons (black arrow); (C) Morphology of mitochondria are preserved by SA (10 μM) under OGD (black arrow). OGD: Oxygen glucose deprivation. EM direct magnification: 50,000 (author's unpublished data).

man studies, no persisting adverse effects related to SA were observed [34]. Rapid onset and transient psychoactive activity indicates that the drug does in fact get into the brain very quickly and has an effect on neural function, which is exactly what a fast acting pleiotropic rescue medication should do. Psychotropic agents may, in fact, be neuroprotective [35] and there is some evidence that drug induced euphoria is associated with reduced cerebral metabolism [36]. There is, as far as we know, no *a priori* reason to assume that the rapid hallucinogenic and euphoric activity is separable from the rapid pleiotropic neuroprotective effects of SA.

Future Research Direction

SA has been shown to possess attributes that make it a very exciting potential stroke rescue therapy. Studies are needed to address the timing of the dosing to achieve significant potential clinical benefit. In particular, how long from onset of stroke can SA be given and still provide significant reduction of infarct and subsequent improvement of stroke outcome? A formulation of SA, specifically for intranasal administration, that is stable and can be directly translated from pre-clinical to clinical use is also needed.

In summary, current evidences indicated that salvinorin A could be a critical game changer in stroke rescue if it can be developed and advanced into clinical practice. The psychoactive effects should not be the huge hurdle it's been perceived as to block the development of this potential life-saving and disability preventing acute rescue strategy for stroke patients.

Conflict of Interests

None.

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