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Resveratrol in epilepsy: preventive or treatment opportunities?

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1. ABSTRACT

Resveratrol has been extensively investigated and has been demonstrated to have antioxidant properties, cancer chemopreventive activity, and the capacity to modulate the hepatic synthesis of triglycerides and cholesterol, among others well established actions. A noteworthy feature of resveratrol is its ability to cross the blood-brain barrier and to exhibit neuroprotective actions, mainly by their capacity to regulate redox pathways as well as the Sirtuin (SIRT) system, which in turn modulates gene transcription, controlling inflammation and apoptosis in the brain. Lately, evidence is accumulating with respect to the synergic effect of resveratrol with antiepileptic drugs and also its antiepileptic activity in various models of seizures. We discuss here recent evidence that strongly suggests that resveratrol acts as an anticonvulsant agent and could be a very effective method for reducing damage in neural tissue and even for preventing seizure development in coadjuvant antiepileptic therapy.

2. NEUROPROTECTIVE EFFECTS OF RESVERATROL

Resveratrol (3,5,4'-trihydroxystilbene) is a natural non-flavonoid polyphenolic compound that can be found in grapevines, pines, and legumes, among other plant species (1,2). Resveratrol has been extensively investigated and has been proposed to have antioxidant properties, cancer chemopreventive activity, and the ability to modulate the hepatic synthesis of triglycerides and cholesterol, among others well established actions (1,3). Its neuroprotective activity and its effects on longevity, inflammation, obesity, and metabolism have been object of numerous studies and we can find an extensive bibliography on its outlandish effects (4,5).

A noteworthy feature of resveratrol is its capacity to cross the blood-brain barrier in animal models (5). Resveratrol increased the activity of antioxidant enzymes in the brains of healthy rats (6,7) and can reach a concentration

peak in the brain 4 hours after intraperitoneal (i.p.) administration (8). The bioavailability of this polyphenol is important for explaining its neuroprotective activity, and time to maximum plasma concentration is reached (Tmax) is a parameter that can provide us with clues concerning its use under acute conditions such as seizures (9).

The brain is the most metabolically active organ in the body in that it has relatively low antioxidant defense and a high content of membrane lipids susceptible to oxidation (10). Therefore, brain tissue maintains a fragile redox homeostasis and neurons are particularly vulnerable to free-radical damage. In seizures, there is an excitotoxic process accompanied by an increase in oxidative processes (11,12). This is initiated by the activation of glutamate receptors with an excessive release of glutamate during seizures, and subsequently calcium overload into the cell that produces a variable decrease in dendritic spines and neuronal cells loss (13,14).

Oxidative molecular processes are activated and the brain cannot protect itself from this oxidative signaling pathway. In such a scenario, the neuroprotective potential of an antioxidant compound such as resveratrol, which is easily and rapidly accessible to the brain, may be enormous. Moreover, the preventive action of dietary administration of resveratrol cannot be ruled out in patients with epilepsy as an adjunct therapeutic strategy to hinder epileptic activity and neurodegeneration (3,4,14).

Trans-resveratrol, and with less potency the isomer cis-resveratrol, are effective antioxidants (15,16) due to their stilbene structure. The two phenol rings present in this molecule means that it is able to scavenge free radicals, including lipid peroxyl and carbon-centered radicals, in addition to Reactive oxygen species (ROS) (17,18).

At this point, recent studies have revealed that resveratrol modulates genes related to redox pathways. It induced the transcriptional co-activator peroxisome proliferator-activated receptor PGC-1a, a master regulator of oxidative stress (OS) and mitochondrial metabolism, in a mouse model of Parkinson disease (PD) (19) and upregulated expression of the transcription factor erythroid 2related factor 2 (Nrf2) in an ischemia rat model (20). The Nrf2-signaling pathway activates the transcription of many genes that are crucial for protection against ROS.

The inflammatory trigger could be a variety of stimuli, including tumor necrosis factor alpha (TNF-a), interleukin-1 (IL-1), T-cell activation signals, and reactive oxygen intermediates, etc., which promote the activation of nuclear factor-kappa beta (NF-??), the central regulator of inflammation (21-23). A number of studies have demonstrated that resveratrol mediates the downregulation of various inflammatory biomarkers such as TNF-a, cyclooxygenase-2 (COX2), inducible citric oxide synthase (iNOS), and interleukins (IL) (23-27). This activity appears to depend on certain structural features of resveratrol, such as the number and position of hydroxyl groups and also the action of resveratrol on SIRT1.

The neuroprotective effects of resveratrol, resulting from its antioxidant activity, have been widely reported (28,29). For instance, resveratrol treatment decreases markers of oxidative damage in *in vivo* and *in vitro* hypoxia-ischemia models, which have a high level of free-radical formation (30).

Additionally, resveratrol possesses other beneficial effects gated to the 5' AMP-activated protein kinase (AMPK) signaling pathway. It shows high capacity to activate AMPK in neuronal cell lines, primary neurons, and the brain (31-33). Furthermore, many of the actions of resveratrol, including mitochondrial biogenesis and neurite outgrowth, depend on the presence of a functional AMPK complex and its upstream regulator, LKB1. Moreover, recent studies have found that resveratrol inhibits phosphodiesterase-4 (PDE4), increasing cyclic adenosine monophosphate (cAMP) levels, which increases AMPK activity and which leads to an increase in the NAD^+/NAD reduced (NADH) ratio and in the activation of SIRT1 (32,33).

Recent studies have focused on resveratrol as one of the possible activators/regulators of the SIRT system, a complicated regulatory biological-response process (5). This highly ontogenically conserved family of genes, denominated silent information regulator genes, has seven members in mammals (SIRT1 through SIRT7) and are widely expressed in a variety of tissues (33). SIRT1 is an nicotinamide adenosine dinucleotide $(NAD)^+$-dependent deacetylating enzyme and is considered a regulatory protein that is modulated by stilbene structures such as resveratrol (28,34). SIRT1 has been shown to target nitric oxide synthase (NOS) for deacetylation, peroxisome proliferator-activated receptor gamma (PGC-1a), FoxO family transcription factors, or p53, thus activating and/or inhibiting their respective roles in controlling inflammation, apoptosis, and modulating gene transcription through epigenetic modulation (35).

Several toxic paradigms, both *in vitro* and *in vivo*, of neuroinflammation have been tested with resveratrol. For instance, resveratrol averts neuronal loss in several animal models in which neurons are exposed to toxic agents. Rats with cognitive loss induced by streptozotocin, which induces a decrease in the central metabolism of glucose jointly with an excitotoxic mechanism of neurotoxicity, improved memory and learning (tested by means of maze negotiation and avoidance of foot shocks) after being administered resveratrol (36,37). In another murine model, in which rats were injected with colchicine (which disrupts microtubules and interferes with axonal and dendritic transport), resveratrol again alleviated the cognitive function deficit, measured by the water-maze test (38). Moreover, in newborn rats, resveratrol reduced neuronal loss after traumatic brain injury (39). Elderly rats were fed pterostilbene, another polyphenol found in grapes and blueberries, performed better in the water-maze test than

those fed a control substance, and pterostilbene provided even greater *in vitro* protection in a chemical-induced neurotoxicity model than resveratrol, as well as in a murine model of senescence (Senescence accelerated mouse prone, SAMP8) (28).

Therefore, the involvement of multiple intracellular resveratrol targets in neuroinflammation appears to be clear, although more studies on structure/activity relationships are required in order to analyze the exact role of this effect on the beneficial activity of resveratrol in the treatment and prevention of neurodegenerative processes in PD or Alzheimer (AD) diseases (39) and also in other neurological pathologies, such as epilepsy.

3. EPILEPSY AND NUTRACEUTICS: STRENGTHS, WEAKNESSES, OPPORTUNITIES, AND THREATS

In contrast to quite homogeneous neurological disorder, such as PD or Huntington disease (HD), the great heterogeneity of disorders denominated "epilepsy" is sometimes overwhelming. Considering the vast diversity of the epilepsies, epileptic syndromes, and related seizure disorders, many efforts have been made to achieve their classification (for a complete and the most widely used classification, see Commission of International League Against Epilepsy (ILAE) (40,41). However, at the cellular and molecular levels, it is feasible to suppose that many of the epileptogenic phenomena share some common mechanisms; therefore, the study and analysis of these molecular mechanisms will lead the elucidation of many aspects of seizure complexity at the basic level.

If finding a cure for such a high impact pathological state is very relevant, it is also very relevant to develop a prophylactic approach. In this aspect, it is widely recognized in the medical community, and also among the general public, that the diet exerts a remarkable influence on the physiological performance of an organism. Recently, research on the effect on the health of the organism of many functional foods that contain bioactive substances, or nutraceutics, has been greatly increased for the complementary treatment of many complex pathologies, such as obesity-related disorders and inflammatory diseases (42) and also of neurodegenerative disorders (43). The effects of some nutraceuticals have received great attention, particularly in regard to epilepsy. This is the case of resveratrol (44), omega-3 fatty acids (45), vitamins, and other dietary supplements (46,47), the use of botanical and herbal remedies (48-50), and the application of complementary alternative medicine (51.52). In general, nutritional therapy is not considered a substitute for anticonvulsant medication. Depending on the effectiveness of the alternative therapy and in selected cases, dosage reductions or suspension of medications should be accepted (47), as well as other beneficial effects that are attractive, such as reducing the adverse effects of antiepileptic drugs, or at least for maintaining general good health (49).

However, there remains a high risk in the noncontrolled use of nearly all of these "natural remedies", because many herbal and dietary supplements may predispose to seizures in individuals without epilepsy and worsen seizure control in those with epilepsy (48,49,53), therefore, the physician must be very cautious and careful when prescribing a combinatorial therapy of anticonvulsants combined with nutraceutics, which may help to modulate the neural activity that leads to seizures.

4. RESVERATROL IN SEIZURES: STATE OF THE ART

In Table 1, we summarized the results obtained in several epileptogenic animal models in which resveratrol has been demonstrated to be capable of exerting a positive influence on convulsive crises and to aid in improving some of their harmful consequences.

Gupta and co-workers (54) reported that trans-resveratrol, administered intraperitoneally (i.p.), played a neuroprotective role in pentylenetretazol (PTZ)-induced seizures, having the adenosinergic mechanism a keyrole in its anticonvulsant activity. In the same study, the authors showed that administration of resveratrol possessed a synergic effect with antiepileptic drugs such as diazepam and sodium valproate. This latter result has been also communicated for other antiepileptics (55).

It is noteworthy that the overexcitation mechanism gated to glutamate receptors is an important mechanism in seizures and that this activation released free-radical production, thus intervention by resveratrol, with well known antioxidant properties presented elsewhere as a potential beneficial approach in epilepsy.

In a kainate model of seizures in adult rat, it was demonstrated that resveratrol can reduce damage induced after toxic administration (56), including cell death in CA1 and CA3 and mossy fiber sprouting. This runs in parallel with the reduced expression of kainate receptors (57). However, Friedman et al. were not able to show clear neuroprotection by resveratrol in neonatal pup rats in which epilepsy was induced by the glutamate receptor agonist, although a pattern of preconditioning neuroprotection can be defined on the basis of moderate protection of CA1 neurons, a region especially sensitive to inflammation and apoptosis in earlier development, but not in CA3 and in other limbic areas (58). Lack of complete limbic-area neuroprotection in rat pups by resveratrol is probably due to a maturation degree of rat brain that is reflexed in reduced free-radical production. Neuronal death is mainly caused in this stage of development by activation of glutamate receptors and calcium entry into hippocampal cells, but in this model, the absence of free-radical production or a reduced implication of OS in the deaths in these animals led to a lack of fully protective activity by resveratrol treatment (58).

The protective role of resveratrol is also described in other models of seizures, such as the IronIII chloride ($FeCl_3$)-induced seizure model of post-traumatic seizures, which are also highly related with OS (59).

Table 1. Effect of resveratrol treatment in epileptogenic animal models

Model	Resveratrol				
Animal	**Convulsive agent**	**Via - Doses**	**Treatment**	**Effect**	**Ref**
Wistar rat of either gender (200–250 g)	FeCl3-induced post-traumatic seizures (FeCl3 i.c. at 5 microl, 100 mM during 5 min)	i.p. - 20 and 40 mg/kg	Administered 30 min before FeCl3 injection and EEG was monitored for 2 h	trans-Resveratrol delayed the onset of the appearance of epileptiform EEG changes. MDA brain levels also significantly reduced in trans-resveratrol-treated animals	59
Wistar rat of either gender (200–250 g)	KA-induced status epilepticus (i.p., 10 mg/kg)	i.p. - 40, 60,or 120 mg/kg	Injected 5 min prior to KA administration and 30 and 90 min after, observed over a 4-h period	Pretreatment alone caused delay in behavioral signs (30 vs. 5 min). Additionally, multiple doses resulted in significant protection, reducing the percentage of incidence in convulsions (from 100 to 15%). Furthermore, level of brain MDA as a marker of OS, was also attenuated with treatment; however, glutathione levels were not significantly different	56
Wistar rat of either gender (200–250 g)	Pentylenetetrazol (PTZ)- induced seizures (i.p., 60 mg/kg)	i.p. - 20, 40 or 80 mg/kg	Administered 20 min prior to convulsive challenge with PTZ	Resveratrol (40 mg/kg) also potentiated the effect of sodium valproate (150 mg/kg) and diazepam (2 mg/kg) against PTZ-induced seizures. When administered together with a subanticonvulsant dose of adenosine (500 mg/kg), significant reduction in percentage of incidence of generalized tonic-clonic convulsions was observed	54
Male Sprague- Dawley rats (260–300 g)	KA (i.p., 8 mg/kg)	i.p. – 30 mg/kg	Injected 30 min prior to KA administration dissolved in 0.5. ml of corn oil	Resveratrol protected against KA-induced neuronal death in hippocampus, and ameliorated KA-induced glial activation. Also suppressed KA-induced activation of astrocytes and microglial cells, acting as free-radical scavenger to protect against neuronal damage	68
Wistar rat of either gender (200–250 g)	KA-induced temporal lobe epilepsy (2.5. ml i. hippocampal from 0.4. mg/ml)	i.g. - 15 mg/kg	Applied once daily for 10 days after initial onset of seizure in acute stage	Resveratrol could significantly decrease number of spontaneous seizures and inhibited frequency of epileptiform discharges. It could protect neurons against kainate-induced neuronal cell death in CA1 and CA3 regions and depressed mossy fiber sprouting. Also, expression level of kainate receptors in hippocampus was reduced	57
Sprague-Dawley rat of either gender P24	Systemic - 7 mg/kg	On diet (1 mg/g) to mothers. To pups, i.p. (2, 20, and 40 mg/g)	Resveratrol on diet to mothers. To pups, daily i.p. was injection from P7–P24	trans-Resveratrol did not ward off convulsant effects of KA during the 3rd postnatal week. However, moderate protection of CA1 neurons, the region most sensitive to inflammation and apoptosis at this age, was observed at highest administered doses. Only modest neuroprotective effect can be achieved during juvenile period with high, but non-toxic, doses of trans-resveratrol in KA model. Antioxidant capacity of trans-resveratrol is limited to protecting juvenile brain from KA seizure-induced injury	58
Wistar rat of either gender (250–300 g)	Pilocarpine (300 mg/kg), with scopolamine (1 mg/kg)	i.p. - 40 mg/kg	Injected 30 min before pilocarpine	There was no effect on percentage of incidence or onset latency of stage 4 seizure behavior. Resveratrol activates SIRT1 and AMPK after status epilepticus and reduces activation of mTOR via AMPK signaling Resveratrol significantly inhibited activation of NF-?? and production of proinflammatory molecules via mTOR pathway	64
Adult male ICR mice (+/– 35 g)	Kainate (i.p., 30 mg/kg)	Systemic - 40 mg/kg	Injected daily for 6 weeks	Combined treatment of resveratrol and exercise attenuated seizure activity and mortality to a greater degree than separated treatment. There is a synergic antioxidant effect of regular exercise and resveratrol, especially in SOD activity	66

Proinflammatory molecules can alter neuronal excitability and affect the physiological functions of glia, and these changes contribute to decreasing seizure threshold and may compromise neuronal survival (60,61). This means that brain inflammation may contribute to neuronal hyperexcitability in epilepsy (62,63).

Within this "inflammatory" context, resveratrol, which is described as a pleiotropic compound, can have a synergic effect that includes more than scavenger or antioxidant effects. In fact, there are a number of works that demonstrate that resveratrol can present anti-inflammatory and neuroprotectant actions on the molecular pathways implicated in the inflammatory process, such as the control of NF-?? activation (32). In this respect, Wang and co-workers recently demonstrated the beneficial effect of resveratrol on pilocarpine-induced seizures in rats through its neuroprotective and anti-inflammatory action (64). The molecular mechanisms that the authors claim in this work are in line with that resveratrol suppresses inflammatory responses induced by seizures partially through AMPK/mammalian target of rapamycin (mTOR) (33). These conclusions are supported by results showing that seizures induced by activating mTOR, which induces NF-?? activation that in turn promotes the expression of inflammatory molecules including iNOS, COX-2, and IL-1ß , are significantly inhibited by resveratrol. The authors conclude that inhibition of NF-?? activation and the production of proinflammatory molecules via the mTOR pathway by resveratrol were in part due to AMP-activated kinase (AMPK) activation (64).

The fine tuning of AMPK and SIRT1 is well defined elsewhere (31,32), and in a the model of pilocarpine seizures, the increase in AMPK activation runs in parallel with an increase in SIRT1 expression, reinforcing the hypothesis that the antioxidant role of resveratrol is accompanied by a specific molecular mechanism involved in inflammation, autophagy, and cell death (55).

On the other hand, it has been observed that regular exercise, whose beneficial effects are also associated with the activation of the PGC-1a-mTOR-SIRT1 axis (62), has a synergic effect on resveratrol against kainate-induced seizures and OS in mice. In particular, the synergistic cooperation of resveratrol and regular exercise was observed

in seizure activity, mortality, and OS, especially in Superoxide dismutase (SOD) activity (66).

Taken together, the evidence suggests that resveratrol acts as an anticonvulsant agent and could be a more efficient method for the prevention of seizure development in coadjuvant antiepileptic therapy (16).

Finally, it is noteworthy that due to the poor bioavailability in the brain described for resveratrol (high metabolism in enterocytes, among others), efforts have been made to overcome these unfavorable pharmacokinetics and lack of druggability (4-6,9,17), for example, lipid-core nanocapsules charged with resveratrol (67). Nanocapsules showed high entrapment of resveratrol and displayed a higher trans-resveratrol concentration in brain, liver, and kidney than that observed for free trans-resveratrol. Thus, the innovative preparation of resveratrol-loaded lipid-core nanocapsules may be used for their potential therapeutic treatment of several diseases, including epilepsy (16,67).

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Abbreviations: $FeCl_3$ = IronIII chloride; EEG, Electroencephalogram; i.c., intracortically; MDA, Malondialdehyde; status epilepticus = epileptic seizure of >30 min; i.p. = intraperitoneally; OS = Oxidative stress; KA = Kainic acid; i.g. = intragastrically; SIRT1 = Sirtuin 1; AMPK = 5' AMP-activated protein kinase signaling pathway; mTOR = mammalian Target of rapamycin; NF-?? = Nuclear factor- kappa beta; ICR = Imprinting control region; SOD = Superoxide dismutase.

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