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Promise of resveratrol for easing status epilepticus and epilepsy

Ashok K. Shetty*

Medical Research and Surgery Services, Veterans Affairs Medical Center, Durham, NC 27705, United States

Department of Surgery (Neurosurgery), Duke University Medical Center, Durham, NC 27710, United States

Abstract

Resveratrol (RESV; 3,5,4'-tri-hydroxy stilbene), a naturally occurring phytoalexin, is found at a high concentration in the skin of red grapes and red wine. RESV mediates a wide-range of biological activities, which comprise an increased life span, anti-ischemic, anti-cancer, antiviral, anti-aging and anti-inflammatory properties. Studies in several animal prototypes of brain injury suggest that RESV is an effective neuroprotective compound. Ability to enter the brain after a peripheral administration and no adverse effects on the brain or body are other features that are appealing for using this compound as a therapy for brain injury or neurodegenerative diseases. The goal of this review is to discuss the promise of RESV for treating acute seizures, preventing the acute seizure or status epilepticus induced development of chronic epilepsy, and easing the chronic epilepsy typified by spontaneous recurrent seizures and cognitive dysfunction. First, the various beneficial effects of RESV on the normal brain are discussed to provide a rationale for considering RESV treatment in the management of acute seizures and epilepsy. Next, the detrimental effects of acute seizures or status epilepticus on the hippocampus and the implications of post-status epilepticus changes in the hippocampus towards the occurrence of chronic epilepsy and cognitive dysfunction are summarized. The final segment evaluates studies that have used RESV as a neuroprotective compound against seizures, and proposes studies that are critically needed prior to the clinical application of RESV as a prophylaxis against the development of chronic epilepsy and cognitive dysfunction after an episode of status epilepticus or head injury.

Keywords

Acute seizures; Cognitive dysfunction; Dentate gyrus; Epilepsy; Epileptogenesis; GABA-ergic interneurons; Hippocampal neurogenesis; Inflammation; Learning and memory; Neurodegeneration; Neuroinflammation; Neuroprotection; Oxidative stress; Polyphenol; Resveratrol; Red wine; Seizures; SIRT1; Status epilepticus; Temporal lobe epilepsy

1. Introduction

Resveratrol (RESV; 3,5,4'-tri-hydroxy stilbene) is a type of polyphenol and an antimicrobial substance synthesized de novo by plants (a phytoalexin). RESV is found in the skin of red grapes and is a component of red wine (Fremont, 2000; Orallo, 2008). The other sources of RESV include raspberries, mulberries, plums, peanuts, bilberries, blueberries, cranberries, Scots pine, and Japanese knotweed. RESV is synthesized instinctively by the above plants as a protection to counter the bacterial and fungal infections, stress and injury (Balestrazzi et

*Division of Neurosurgery, Box 3807, Duke University Medical Center, Durham NC 27710. Tel.: 919 286 0411x7096. Ashok.Shetty@Duke.Edu..

al., 2009; Maddox et al., 2010). RESV received substantial notice with the emergence of “French paradox”, which is portrayed by the reduced prevalence of cardiovascular diseases in the red wine drinking southern France population notwithstanding eating foods that are rich in saturated fats (Vidavalur et al., 2006). Although RESV subsists as both *cis-* and *trans*isomeric forms, the *trans*-isomer is the steady form of RESV, which is also the isomer that plays a role in nearly all biological actions of RESV (Fremont, 2000). RESV mediates a variety of biological activities which comprise extension of the life span even when fed a high caloric diet and cancer prevention (Howitz et al., 2003; Wood et al., 2004; Baur et al., 2006; Baur & Sinclair, 2006; Orallo, 2008). Studies in animal models also imply a number of other beneficial health effects of RESV, which comprise anti-ischemic, antiviral, anti-oxidant and anti-inflammatory properties (Belguendouz et al., 1997; Jang et al., 1999; Manna et al., 2000; Sato et al., 2000; Kraft et al., 2009; Campagna & Rivas, 2010; Robich et al., 2010; Sun et al., 2010). Furthermore, RESV shows promise for delaying the onset of a variety of age-related diseases (Orallo, 2008; Rossi et al., 2008; Karuppagounder et al., 2009).

Pertaining to the central nervous system, multiple cell culture investigations and *in vivo* studies in animal models of neurodegenerative diseases/brain injury point out that RESV is a potent neuroprotective compound. First, in cell culture studies, RESV treatment reduced: (i) ethanol induced neuronal cell death (Sun et al., 1997); (ii) sodium nitroprusside induced hippocampal cell death and intracellular reactive oxygen species (ROS) accumulation (Bastianetto et al., 2000); (iii) neuronal cell death in the presence of amyloid beta-peptide, a neurotoxic peptide believed to have a role in the pathogenesis of Alzheimer's disease (Jang & Surh, 2003; Han et al., 2004); and (iv) the loss of dopaminergic neurons in rat primary midbrain neuron–glial cultures treated with lipopolysaccharide (LPS) via anti-inflammatory activity (Zhang et al., 2010). Second, in animal models of stroke, RESV pre-treatment provided neuroprotection via its antioxidant actions and induction of heme oxygenase 1 (Sinha et al., 2002; Wang et al., 2002; Baur & Sinclair, 2006; Sakata et al., 2010). Third, RESV treatment provided neuroprotection and functional recovery in a rat model of spinal cord injury via its anti-oxidant, anti-apoptotic and anti-inflammatory actions (Liu et al., 2010). Fourth, oral administration of RESV attenuated neuronal damage and neurological dysfunction in a rat model of multiple sclerosis likely via anti-inflammatory activity (Shindler et al., 2010). Recent studies imply that p^{38} mitogen-activated protein kinase (p^{38} MAPK) cascade is a key signal transduction pathway for eliciting the anti-inflammatory action of RESV through transcriptional induction of macrophage inhibitory cytokine-1 (Golkar et al., 2007; Paul et al., 2009). Fifth, RESV treatment provided neuroprotection in animal models of Huntington's disease via activation of Ras-extracellular signal-regulated kinase (ERK; Maher et al., 2010). Sixth, RESV attenuates behavioral impairments and reduces cortical and hippocampal neuron loss in a rat controlled cortical impact model of traumatic brain injury (Singleton et al., 2010). Thus, the capability of RESV for vigorous neuroprotection has been detected in animal models of multiple neurodegenerative diseases. Besides, its ability to traverse the blood–brain-barrier after peripheral administration (Mokni et al., 2007) and a lack of undesirable consequences on the brain are other characteristics that present this compound as attractive for therapeutic use in neurodegenerative disorders (Baur & Sinclair, 2006). Additionally, the activity of RESV in the brain after peripheral administration (including after an oral administration) can last up to 4 h (Wang et al., 2002; Abd El-Mohsen et al., 2006). Taken together, it is clear that RESV is a potent neuroprotective compound. Yet, the relevance of the above findings to clinical situations needs to be validated.

The purpose of this review is to discuss the promise of RESV administration for treating acute seizures, preventing acute seizure or status epilepticus (SE) induced chronic epilepsy, and for easing chronic epilepsy characterized by spontaneous recurrent motor seizures. The

first section will discuss the known effects of RESV on the normal brain, which support the use of RESV for treating acute seizures and epilepsy. The second section summarizes the detrimental effects of acute seizures or status epilepticus (SE) on the hippocampus and the implications of post-SE changes in the hippocampus towards the occurrence of chronic epilepsy and cognitive dysfunction. The final segment evaluates studies that have used RESV as a neuroprotective compound against seizures and epilepsy. Furthermore, critical studies that are needed before considering RESV as a prophylaxis treatment against chronic epilepsy development and cognitive dysfunction after an initial precipitating event such as SE or head injury are discussed.

2. Resveratrol treatment and normal brain function

Because of a higher degree of oxygen consumption and availability of relatively lower levels of antioxidant defense enzymes, the adult brain is very vulnerable to free radical mediated damage (Halliwell, 2006). Studies on the effects of RESV treatment on normal brain function suggested many beneficial effects, which include maintenance of the mitochondrial function, neuroprotective properties, preservation of cognitive function and anti-excitatory properties. These issues are briefly discussed in the following sections to support the use of RESV for treating acute seizures and epilepsy.

2.1. Resveratrol and mitochondrial function

Zini et al. (1999) showed that RESV decreases complex III activity in the mitochondria through competition with coenzyme Q. This mode of action imparts beneficial effects as complex III is the site where ROS are generated. RESV was also able to scavenge the superoxide anion generated from the rat forebrain mitochondria in a concentration dependent manner (Zini et al., 1999). Thus, by reducing complex III activity, RESV could both oppose the production of ROS and scavenge the ROS that were produced. Furthermore, a follow up study by the same group (Zini et al., 2002) demonstrated that RESV inhibits the release of cytochrome c (an initial step of mitochondrial apoptosis) and decreases the superoxide anion production, which in turn protected the mitochondrial membranes in an anoxia-reoxygenation model. Another study using a prototype of anoxia-reoxygenation applied to suspensions of mitochondria isolated from the rat cortex, confirmed the effects of RESV on cytochrome c release and showed that RESV blocks ATP generation (Tillement, 2001). Thus, RESV intake appears to be useful for preserving mitochondrial function through antioxidant properties, actions on complex III, and a membrane stabilizing effect (Fig. 1).

2.2. Resveratrol and lipid peroxidation

Inhibition of the lipid peroxidation by RESV has been demonstrated in several studies (Lu et al., 2002; Zhuang et al., 2003; Mokni et al., 2007). In one of the studies, intraperitoneal administration of RESV in a healthy normal rat decreased brain malondialdehyde (MDA) levels and increased brain superoxide dismutase, catalase and peroxidase activities (Mokni et al., 2007). Optimal effects were seen with the RESV dose of 12.5 mg/kg body weight (bw). Another study using neuronal cell cultures demonstrated that RESV treatment induces heme oxygenase 1 activity with no detectable toxic effects (Zhuang et al., 2003). Because heme levels increase inside cells after stroke and heme (iron-protoporphyrin IX) is considered a pro-oxidant, its rapid degradation by heme oxygenase is believed to be neuroprotective. From this perspective, increased heme oxygenase activity is likely one of the mechanisms by which RESV functions as a neuroprotective compound. Thus, RESV exerts neuroprotective properties by regulating several detoxifying enzymes (Fig. 1).

2.3. Resveratrol and phosphorylation of MAP kinases and AMP kinase activity

Using human neuroblastoma SH-SY5Y cells in vitro, Tredici et al. (1999) showed that RESV induces phosphorylation of several MAP kinases which include extracellular signal-regulated kinase 1 (ERK1) and ERK2. As MAP kinases are critical for different aspects of signal transduction in cells, and phosphorylation of ERK2 is vital for synaptic changes in response to memory and learning processes, effects of RESV on MAP kinases are likely useful for preventing dementia. Indeed, epidemiological studies suggest that moderate wine intake decreases the incidence of dementia (Mehlig et al., 2008). Moreover, proteomics analyses of the rat brain proteins following RESV treatment suggests that RESV mediated protection against dementia involves prevention of the loss of proteins that are implicated in cognitive disorders (Kim et al., 2006). Furthermore, RESV stimulates AMP kinase activity in Neuro2a cells and primary neurons in vitro, and neurons in the adult brain (Dasgupta & Milbrandt, 2007). RESV mediated AMPK activation promoted robust neurite outgrowth in Neuro2a cells, which could be blocked by genetic and pharmacologic inhibition of AMPK. Further analyses also provided evidence that RESV induces mitochondrial biogenesis via AMPK activation. Thus, phosphorylation of MAPKs and activation of AMPK by RESV in neurons likely helps in the maintenance of cognitive functions and provides neuroprotection (Fig. 1).

2.4. Resveratrol and electrical activity of hippocampal neurons

Using a prototype of rat hippocampal neuronal cultures, Gao and Hu (2005) demonstrated that superfusion of RESV could reversibly inhibit the delayed rectifier (I(K)) and fast transient K(+) current (I(A)). As voltage-gated K(+) channels have been implicated in neuronal apoptosis, it is possible that inhibition of voltage-activated K(+) currents by RESV contributes to its neuroprotective effects. Furthermore, Li et al. (2005) using extracellular recording techniques in hippocampal slices demonstrate that RESV inhibits neuronal discharges in rat hippocampal CA1 area. Specifically, application of RESV reduced the spontaneous discharge rate in majority of neurons in a dose dependent manner. Furthermore, RESV suppressed epileptiform discharges in slices mediated by several compounds, which include L-glutamate, L-type calcium channel agonist, and nitric oxide synthase inhibitor L-NAME. Additionally, a study by Gao et al. (2006) showed that perfusion with RESV causes a concentration-dependent reversible inhibition of field excitatory postsynaptic potentials via suppression of glutamate-induced currents in postsynaptic CA1 pyramidal neurons, suggesting inhibition of postsynaptic glutamate receptors by RESV. Thus, RESV has the ability to inhibit the electrical activity of hippocampal pyramidal neurons through several mechanisms. This anticonvulsant property makes RESV ideal as a neuroprotective agent against acute seizures (Fig. 1).

2.5. Resveratrol and oxidative stress

Okawara et al. (2007) examined the neuroprotective effect of RESV on dopaminergic neurons in organotypic slice cultures prepared from the midbrain. They demonstrated that RESV prevents the loss of dopaminergic neurons when slice cultures were treated with a dopaminergic neurotoxin, 1-methyl-4-phenyl pyridinium. They also found that RESV provides concentration-dependent neuroprotective effects against a mitochondrial complex IV inhibitor sodium azide, and a microglia-activating agent thrombin. These beneficial effects appeared to be due to a direct antioxidant property of RESV, as inhibitors of silent mating type information regulation 2 homolog 1 (SIRT1, a class III histone deacetylase) did not attenuate the protective effect of RESV, and RESV treatment reduced the accumulation of ROS, depletion of cellular glutathione, and cellular oxidative damage. In another study, RESV pre-treatment effectively protected against cadmium-induced lipid peroxidation and ameliorated the adverse effect of cadmium (Eybl et al., 2006). Thus, RESV is an effective

antioxidant, which makes it suitable as a neuroprotective compound against acute seizures or SE.

2.6. Resveratrol and inflammation

A study examined the effects of RESV administration on nitric oxide and tumor necrosis factor- α (TNF- α) production in cultured microglia that are activated through lipopolysaccharide (LPS) treatment (Bi et al., 2005). While the microglial cultures exposed to LPS alone exhibited increased levels of TNF- α and NO, microglial cultures exposed to LPS and RESV displayed no significant increases in TNF- α and NO. Additional analyses revealed that RESV administration suppressed LPS-induced expression of iNOS and phosphorylation of p38 MAPKs in microglial cells. Thus, RESV can potentially suppress proinflammatory responses of microglia. Considering these, it appears that RESV administration would be beneficial for curtailing the inflammatory reaction in neurodegenerative diseases. This is particularly applicable to conditions where significant microglial activation is one of the pathological changes such as after acute seizure or SE induced brain injury.

2.7. Resveratrol and activation of SIRT1

SIRT1, a nuclear protein and the mammalian equivalent of the silent information regulator 2 (SIR2) that promotes longevity in yeast, flies and nematodes, has a role in the regulation of key metabolic and physiological processes (Chung et al., 2010). SIRT1 is a class III histone deacetylase (HDAC) and believed to underlie the health benefits of caloric restriction, a diet that defers aging and neurodegeneration in mammals (Kim et al., 2007). Studies demonstrate that activation of SIRT1 by polyphenols such as RESV has multiple favorable outcomes (Chung et al., 2010). These include regulation of the oxidative stress, inflammation, cellular senescence, autophagy, apoptosis, differentiation, stem cell pluripotency, metabolism, and mitochondrial biogenesis (Chung et al., 2010). SIRT1 knockout or knockdown results in an increased activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and proinflammatory cytokine release. NF- κ B, a protein complex that controls the transcription of DNA, is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation and bacterial or viral antigens. Incorrect regulation of NF- κ B has been linked to cancer, inflammatory and autoimmune diseases (Brasier, 2006; Perkins, 2007). Interestingly, stimulation of SIRT1 by activators such as RESV inhibits NF- κ B-mediated inflammatory mediators release (Chung et al., 2010). Studies have also shown that SIRT1 can interact, deacetylate and activate FOXO3, a transcription factor that regulates a number of cellular responses, such as the cell cycle arrest, cellular senescence, proliferation, resistance to oxidative stress and apoptosis (Brunet et al., 2004; Chung et al., 2010). SIRT1 plays an important role in regulating autophagy, which is a process important for the turnover of cellular organelles and proteins to maintain the cell homeostasis. Indeed, SIRT1-deficient mice have accumulation of damaged organelles and disruption of homeostasis (Lee et al., 2008). Thus, activation of SIRT1 can mediate multiple beneficial health outcomes and enhanced physiological functions. RESV is the first polyphenolic compound that has been shown to activate SIRT1 (Cohen et al., 2004; Kaeberlein et al., 2005; Baur et al., 2006). Recent in vivo studies have revealed that RESV supplementation leads to increased activity of mitochondria and peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α ; a transcriptional coactivator that regulates the genes involved in energy metabolism), with a concomitant decrease in their acetylation (Baur & Sinclair, 2006; Lagouge et al., 2006). SIRT1-mediated deacetylation of PGC-1 α by RESV acts as a regulator of mitochondrial energy balance and biogenesis. Hence, activation of SIRT1 via RESV appears to be beneficial for treating various chronic inflammatory diseases (Yeung et

al., 2004; Milne et al., 2007; Rajendrasozhan et al., 2008; Chung et al., 2010; Singh et al., 2010).

Pertaining to the brain, SIRT1 affects different processes that are potentially involved in the maintenance of brain integrity. These include chromatin remodeling, DNA repair, cell survival, and neurogenesis (Michan et al., 2010). Absence of SIRT1 impairs cognitive abilities, including immediate memory, classical conditioning and spatial learning, and synaptic plasticity (Michan et al., 2010). Another recent study has also shown that SIRT1 modulates synaptic plasticity and memory formation (Gao et al., 2010). Activation of SIRT1 enhanced whereas loss of SIRT1 function impaired synaptic plasticity in this study. Further analyses revealed that these effects were mediated through post-transcriptional regulation of cAMP response-element binding protein (CREB) expression by a brain-specific microRNA, miR-134. Under normal conditions, SIRT1 limits the expression of miR-134 through a repressor complex containing the transcription factor YY1 (Gao et al., 2010). Additional characterization unraveled that SIRT1 deficiency leads to an increased expression of miR-134, which induces downregulation in the expression of CREB as well as the neurotrophic factor BDNF and impairs synaptic plasticity (Gao et al., 2010). Thus, SIRT1 has a direct role in regulating cognitive function in the brain. Indeed, a study has demonstrated that administration of RESV in the inducible p25 transgenic mice (a model of Alzheimer's disease and amyotrophic lateral sclerosis) reduced hippocampal neurodegeneration, prevented learning impairment and decreased the acetylation of the known SIRT1 substrates, PGC-1 α and p53 (Kim et al., 2007). Overall, it appears that activation of SIRT1 through compounds such as RESV has great importance for providing neuroprotection and alleviating cognitive dysfunction observed in various neurodegenerative disorders including the temporal lobe epilepsy (TLE) (Fig. 1).

3. Acute seizures or status epilepticus and development of chronic temporal lobe epilepsy

Status epilepticus (SE) is an emergency condition typified by prolonged seizure activity, which affects > 150,000 Americans every year with ~20% mortality (Sirven & Waterhouse, 2003; Boggs, 2004). In addition, a significant percentage of SE-survivors exhibit morbidity typified by cognitive impairments and/or an increased risk for chronic epilepsy. The first line antiepileptic drugs (AEDs) such as benzodiazepines and phenytoin used for the treatment of SE are ineffective in ~40% of patients (Shaner et al., 1988; Sirven & Waterhouse, 2003; Knake et al., 2009). The AEDs also have adverse side effects and do not seem to alter the long-term detrimental effects of SE, such as cognitive impairments and chronic epilepsy. Hence, efficient alternative therapies are necessary for preventing SE-induced mortality and morbidity.

3.1. Long-term implications of SE-induced hippocampal injury on learning and memory

The hippocampus is highly vulnerable to SE-induced injury (Sankar et al., 1998; Sloviter et al., 2003). This is exemplified by substantial damage to the hippocampus observed after SE elicited by chemoconvulsants such as kainic acid (KA) or pilocarpine (Dube et al., 2001; Bengzon et al., 2002; Rao et al., 2006). The pattern and extent of hippocampal neurodegeneration in a rat model of SE induced through i.p. KA administration are illustrated in Fig. 2. Acute seizures or SE induced by KA in rat leads to degeneration of fractions of dentate hilar neurons (including the excitatory mossy cells) and CA1 and CA3 pyramidal neurons (Hellier et al., 1998; Hattiangady et al., 2004; Rao et al., 2006; Rao et al., 2007), and a significant inflammation (Hattiangady et al., 2004; Hattiangady & Shetty, 2008). An example of inflammation characterized by the presence of a large number of activated microglial cells after KA-induced SE in a rat model is shown in Fig. 3.

Hippocampal injury inflicted by SE can lead to impairments in learning and memory function (Liu et al., 2003; Alessio et al., 2004a; Strine et al., 2005; Groticke et al., 2007; Jones et al., 2008; Lenck-Santini & Holmes, 2008). Studies in animal models show that SE impairs spatial learning and memory function. This was evidenced by: (i) a longer latency to the criterion and more reference errors in a radial arm-maze test; and (ii) longer escape latencies and deficient memory for finding the platform location in a Morris water maze test (Letty et al., 1995; Rutten et al., 2002; Mikati et al., 2004; Sayin et al., 2004; Detour et al., 2005). Fig. 4 illustrates spatial learning and memory impairments in a rat model after KA-induced SE. The observations are consistent with the clinical reports that memory difficulties are a frequent cognitive complaint in patients after SE and in patients with chronic epilepsy (Neville et al., 2007; Vannest et al., 2008). Thus, SE induces persistent cognitive dysfunction. As these impairments are associated with hippocampal neurodegeneration, apt interventions that provide maximal neuroprotection during and shortly after SE might prevent or greatly diminish these adverse effects on learning and memory function.

3.2. Effects of SE on the behavior of neural stem/progenitor cells

In the hippocampus, new neurons are added to the granule cell layer of the dentate gyrus (DG) all through life. This occurs because of continued proliferation of neural stem/progenitor cells (NSCs) residing in the subgranular zone (SGZ) of the DG (Eriksson et al., 1998; Gould & Gross, 2002; Song et al., 2002; Arous et al., 2005). Many studies advocate a linkage between the amount of DG neurogenesis and the hippocampal-dependent cognitive functions (van Praag et al., 2002; Aimone et al., 2006; Kee et al., 2007; Imayoshi et al., 2008). For example, there is an association between a decreased DG neurogenesis and impairments in some of the hippocampal-dependent learning and memory functions (Drapeau et al., 2003; Rola et al., 2004; Siwak-Tapp et al., 2007; Dupret et al., 2008; Jessberger et al., 2009). The various conditions that inflict hippocampal injury such as after an episode of acute seizures, ischemia, stroke or hypoxia greatly enhance DG neurogenesis for a certain period of time (Parent et al., 1997; Choi et al., 2003; Felling & Levison, 2003). Pertaining to seizures, multiple studies now corroborate that the reaction of DG neurogenesis swerves noticeably between the initial and delayed stages after acute seizures. Acute seizures or SE greatly enhance NSC proliferation and result in a greatly increased DG neurogenesis (Bengzon et al., 1997; Parent et al., 1997; Gray & Sundstrom, 1998; Nakagawa et al., 2000; Ekdahl et al., 2001; Hattiangady et al., 2004) (Fig. 5). The discharge of NSC mitogenic factors from dying neurons, deafferented granule cells and reactive glia is believed to be one of the underlying factors promoting this surge in neurogenesis, as the concentration of several neurotrophic factors is elevated in the hippocampus after SE/brain injury (Lowenstein et al., 1993; Shetty et al., 2003, 2004). Acute hyperexcitability and increased GABA levels following SE could be another factor promoting increased neurogenesis, as GABA is mitogenic to NSCs (Ge et al., 2007). It takes about 2–3 weeks for normalization in the rate of NSC proliferation and return to the baseline-level of neurogenesis after SE (Parent et al., 1997; Nakagawa et al., 2000). Addition of a large number of new neurons to the granule cell layer of the DG after SE appears to be beneficial. This is because, newly born neurons that are added to the granule cell layer after an episode of SE or acute seizures tend to exhibit reduced excitability, which may contribute towards decreasing the overall hyperexcitability of the DG after SE (Jakubs et al., 2006).

However, the presence of anomalous migration of a fraction of newly born granule cells into the dentate hilus and/or the molecular layer after SE (Fig. 5 [C1]) is considered to be detrimental (Houser, 1990; Scharfman et al., 2000, 2002a,b; McCloskey et al., 2006; Parent et al., 2006; Parent, 2007; Shetty & Hattiangady, 2007). Loss of reelin (a secreted migration guidance cue) expression after SE has been suggested to be the reason for this aberrant

integration of newly born dentate granule cells into ectopic locations (Gong et al., 2007). It has been shown that newly born granule cells that drift off uncharacteristically into the dentate hilus get incorporated abnormally with the CA3 network (Scharfman et al., 2000), get activated when spontaneous seizures occur (Scharfman et al., 2002b), and respond to stimulation of the hippocampal perforant path afferents from the entorhinal cortex with a longer latency to onset of evoked responses (Scharfman et al., 2003). Moreover, these ectopically placed granule cells establish afferent connectivity with mossy fiber terminals (i.e. with axons of granule cells in the granule cell layer of the DG; Pierce et al., 2005), exhibit natural eruptions of action potentials (Scharfman et al., 2000) and seem to be a factor in spontaneous recurrent seizures that occur in chronic epilepsy (Jung et al., 2004; McCloskey et al., 2006). From the above, it is clear that SE-induced abnormal DG neurogenesis promotes development of an aberrant circuitry in the DG. This aberrant circuitry is believed to contribute towards the evolution of SE into chronic epilepsy. Hence, it will be critical to examine in future studies whether the most efficacious neuroprotective treatments can also thwart seizure-induced abnormal neurogenesis.

The overall DG neurogenesis declines substantially at delayed time-points after SE (i.e. when spontaneous seizures occur) (Hattiangady et al., 2004; Kuruba & Shetty, 2007; Hattiangady & Shetty, 2008; Kuruba et al., 2009)(Fig. 6). A recent study demonstrated that declined neurogenesis in chronic epilepsy is not due to decreased production of new cells or poor survival of newly born cells. Rather, it is due to a dramatically decreased neuronal differentiation of newly born cells. It turns out that, in chronic epileptic conditions, most of the newly born cells differentiate into glia rather than into neurons (Hattiangady & Shetty, 2010; Fig. 7). Considering that chronic epilepsy is also associated with substantially decreased levels of several neurotrophic factors including BDNF and FGF-2 (Hattiangady et al., 2004; Shetty et al., 2004), it is plausible that changes in DG milieu contribute to the declined neuronal differentiation of newly born cells. Furthermore, both decrease in DG neurogenesis and ectopic migration of newly born granule cells were more pronounced in rats exhibiting greater frequency of spontaneous recurrent seizures. Additionally, a vast majority of newly born neurons in chronically epileptic hippocampi displayed basal dendrites (Fig. 6), another feature that is believed to contribute towards the establishment of recurrent excitatory circuitry (Ribak et al., 2000; Shapiro & Ribak, 2006; Hattiangady & Shetty, 2008). In view of the importance of DG neurogenesis in hippocampal-dependent learning and memory functions, it is likely that the various hippocampal-dependent learning and memory deficits observed in chronic epilepsy are linked at least partially to the declined DG neurogenesis (Brown-Croyts et al., 2000; Oddo et al., 2003; Alessio et al., 2004a,b). Thus, it will be important to investigate in future studies whether the ideal neuroprotective therapies have the ability to maintain a normal level of hippocampal neurogenesis and cognitive function in the chronic phase after injury or SE.

3.3. Effects of SE on hippocampal gamma-amino butyric acid positive (GABA-ergic) interneuron population

Loss of GABA-ergic interneurons after SE/brain injury is believed to have a significant role in epileptogenesis, as it can lead to a reduction of GABA-mediated inhibition and promote seizures. Multiple studies have analyzed the potential loss of GABA-ergic interneurons in various models of SE and brain injury. Studies that focused on early time-time points mostly suggested the resistance of GABA-ergic interneurons to SE/brain injury (Franck et al., 1988; Davenport et al., 1990a,b; Morin et al., 1998; Williamson et al., 1999). However, studies that analyzed the subclasses of interneurons expressing different calcium binding proteins and neuropeptides at delayed time-points after SE/brain injury showed a substantial loss of these interneurons (Sperk et al., 1986; Shetty & Turner, 1995a,b; Kobayashi et al., 2003). Studies quantifying the numbers of interneurons expressing the GABA synthesizing enzyme

glutamate decarboxylase-67 at 1–6 months after KA-induced seizures/injury showed substantial reductions in their number throughout the hippocampus (Shetty & Turner, 2000, 2001; Shetty et al., 2009). The upper panel of Fig. 8 illustrates the loss of a subclass of GABA-ergic interneurons expressing the neuropeptide Y in the hippocampus of a rat that underwent SE. The above findings imply that reduced number of GABA-ergic interneurons likely contributes to the decreased functional inhibition observed during the chronic phase after SE. It is also possible that decreased inhibition is one of the factors contributing to the occurrence of spontaneous seizures during the chronic phase after SE (Sloviter, 1987; Cornish & Wheal, 1989; Sloviter, 1991; Obenaus et al., 1993; Houser & Esclapez, 1996; Dudek & Spitz, 1997; Bernard et al., 1998). This premise is supported by anticonvulsant actions observed after the administration of drugs that increase synaptic GABA (Treiman, 2001), or grafting of cells that synthesize and release GABA in epilepsy models (Loscher et al., 1998; Gernert et al., 2002; Thompson, 2005; Castillo et al., 2006; Hattiangady et al., 2008; Waldau et al., 2010). Thus, preservation of the GABA-ergic interneuron population after an episode of SE via neuroprotective interventions appears useful for preventing chronic epilepsy after SE (Coulter, 1999; Ben-Ari, 2006; Richardson et al., 2008).

3.4. Consequences of SE on synaptic reorganization in the dentate gyrus

Degeneration of a fraction of dentate hilar cells and CA3 pyramidal neurons, the target cells of granule cell axons (mossy fibers) is distinctively seen after an episode of SE/hippocampal injury induced by chemoconvulsants such as KA. This results in the evolution of an abnormal hippocampal circuitry typified by the sprouting of mossy fibers into the dentate supragranular layer (DSGL; Fig. 8 [lower panel]), analogous to the alteration observed in the human TLE (Houser et al., 1990; Babb et al., 1991; Mathern et al., 1996; Shetty & Turner, 1999). The aberrant mossy fiber sprouting (MFS) has been considered as one of the hallmarks after an episode of SE or in TLE (Houser et al., 1990; Franck et al., 1995). Studies on this anomalous sprouting in various animal prototypes of TLE hold up the hypothesis that the abnormal dentate MFS causes granule cells to stimulate one another and is the center of seizure activity, which are revealed by the following observations. To begin with, the sprouted mossy fibers form new asymmetric (excitatory) synapses on dendritic spines of granule cells that are not their parent neurons, which implies a strong influence of MFS on the circuit formation (Buckmaster et al., 2002; Koyama & Ikegaya, 2004). Furthermore, exogenous glutamate treatment to the dentate molecular layer results in excitatory post-synaptic currents or excitatory post-synaptic potentials in granule cells that are situated away from the treated site in epileptic rats (Molnar & Nadler, 1999; Lynch & Sutula, 2000). Moreover, antidromic stimulation of the granule cells in acute hippocampal slices from epileptic rats evokes prolonged seizure-like bursts of population spikes in the granule cell layer, when inhibition is depressed and/or the concentration of extracellular potassium is increased (Wuarin & Dudek, 1996; Okazaki et al., 1999). Besides, in animals with abnormal MFS, a single stimulation of the entorhinal-dentate (perforant) pathway generates 3–12 successive population spikes in contrast to the single spike/stimulus observed in the saline treated controls (Patrylo et al., 1999). This implied that the synaptic input from the entorhinal cortex is converted to epileptiform bursts through mossy fiber recurrent circuits (Koyama & Ikegaya, 2004). Additionally, in epileptic animals, an association has been identified between the progression of aberrant MFS and the frequency and intensity of spontaneous recurrent seizures (Sutula et al., 1988).

From the above, it appears that the aberrant MFS is closely linked to spontaneous recurrent seizures in TLE. However, some studies contradict this notion based on the observations that: (i) no correlation exists between the aberrant MFS and the first spontaneous seizure after SE (Nissinen et al., 2001); (ii) the presence of aberrant MFS is not a pre-requisite for epileptogenesis in postnatal models of SE (Bender et al., 2003); (iii) the MFS after SE also

promotes an increased inhibition of the DG (Sloviter, 1992); and (iv) new excitatory circuits after SE develop in the CA1 region as well (Shao & Dudek, 2005). Thus, it remains to be determined whether the MFS is a cause or result of epilepsy. Nevertheless, because the sprouted mossy fibers make excitatory connections with the dendrites of granule cells, it is plausible that the aberrant MFS contributes to the chronic state of TLE (Zhang et al., 2002; Koyama & Ikegaya, 2004). Indeed, several studies suggest that the DG with aberrant MFS has increased seizure susceptibility (Mathern et al., 1993, 1996; Sutula, 2002; Nadler, 2003; Santhakumar et al., 2005). Thus, deterrence of aberrant MFS is likely to be vital for either blocking or reducing the intensity of DG hyperexcitability and spontaneous recurrent seizures after SE. Such prevention would however require considerable neuroprotection to dentate hilar neurons as well as CA3 pyramidal neurons during SE (Nadler, 2003; Shetty et al., 2003; Cavazos et al., 2004; Shetty et al., 2005; Dudek & Sutula, 2007; Nadler et al., 2007).

3.5. Evolution of SE into chronic epilepsy characterized by spontaneous seizures

In most cases, SE leads to the development of chronic epilepsy after a delay (Dube et al., 2001; Bengzon et al., 2002). In a F344 model of SE, virtually all rats that exhibit continuous stages III–V seizures for over 3 h after the KA administration acquire chronic epilepsy characterized by spontaneous recurrent motor seizures (Rao et al., 2006). In this study, each KA-treated rat displayed over 2.0 spontaneous seizures per hour at 3–5 months post-SE. The duration of individual seizures was ~61 s at 4 and 5 months post-SE.

Electroencephalographic (EEG) recordings from the cortex (via a pre-implanted epidural metal electrode) and the hippocampus (via a pre-implanted intrahippocampal stainless steel electrode) confirmed robust chronic epilepsy in these animals. Fig. 9 illustrates an EEG trace during a stage IV/V spontaneous seizure (along with electrographic activities both before and after a spontaneous seizure). Thus, the various epileptogenic changes that ensue after SE (including an abnormal pattern of neurogenesis in the dentate gyrus, loss of GABA-ergic interneurons, and an aberrant mossy fiber sprouting) eventually lead to the development of chronic epilepsy characterized by spontaneous recurrent seizures.

3.6. Significance of hippocampal neuroprotection against SE

Neuroprotection has been examined in animal models of SE. It is believed that seizure-induced hippocampal neuron loss, and the ensuing changes in NSC behavior, neurogenesis and circuitry contribute to impairments in new learning, formation of new memories and chronic epilepsy development. Therefore, application of neuroprotective strategies early after the onset of SE is considered beneficial (Ebert et al., 2002). In animal models of SE, the major neuronal damage occurs in structures belonging to the circuit of initiation and maintenance of seizures (i.e. the dentate gyrus and the hippocampus), though some damage also occurs in the propagation areas such as the entorhinal, perirhinal and piriform cortices, and thalamic and amygdalar nuclei. Certain antiepileptic drugs and NMDA receptor blockers protect fractions of hippocampal pyramidal neurons from dying following acute seizures but fail to prevent the loss of dentate hilar neurons and GABA-ergic interneurons (Andre et al., 2001; Brandt et al., 2003; Kapur, 2003; Rigoulot et al., 2004). Ideal neuroprotection strategies after the onset of SE should be capable of: (i) considerably rescuing all types of hippocampal neurons that are vulnerable to seizures; (ii) suppressing the abnormal behavior of NSCs and their progeny in the DG; (iii) preventing or diminishing the aberrant synaptic reorganization in the DG and other regions. If these requirements are met, it may be possible to avoid both hippocampal dysfunction and chronic epilepsy after SE.

4. Efficacy of RESV administration against acute seizures and epilepsy

4.1. Neuroprotective effects of RESV against excitotoxic brain injury and acute seizures

A study by Virgili and Contestabile (2000) was the first to suggest a neuroprotective property for RESV against excitotoxic brain injury. They compared the effect of systemic administration of an excitotoxin kainic acid (KA) between young adult rats that were chronically treated with RESV and control young adult rats. They found that chronic RESV treatment prior to the KA administration considerably reduced the damage caused by KA in the olfactory cortex and the hippocampus. Following this, a study demonstrated the protective effect of RESV pretreatment on KA induced seizures and oxidative stress (Gupta et al., 2002). They found that a single dose of RESV (at 40 mg/kg i.p.) five-minutes prior to KA treatment (10 mg/kg i.p.) increased the latency to convulsions but was unable to completely inhibit the convulsions. However, with multiple doses of RESV treatment (i.e. at 5 min prior to KA injection and at 30 and 90 min post-KA injection), the incidence of convulsions was significantly reduced. The above RESV treatment regimen also inhibited the KA-injury related increases in the level of MDA, suggesting that antioxidant function is one of the mechanisms by which RESV mediates neuroprotection against excitotoxic injury and acute seizures.

Furthermore, a study has shown neuroprotection when RESV was administered prior to intracortical placement of FeCl₃ (Gupta et al., 2001). In the absence of RESV treatment, FeCl₃ treated animals exhibited significant epileptiform EEG discharges and increased levels of the oxidative stress marker MDA in the brain tissue. However, in animals that received RESV (20 or 40 mg/kg i.p.) 30 min prior to FeCl₃ treatment, the onset of the epileptiform EEG discharges was delayed and MDA levels were reduced. However, it was unclear whether the above protective effects are adequate for preventing neurodegeneration in the hippocampus, a learning and memory center of the brain that plays an important role in the development of chronic TLE following injury. A subsequent study investigated this issue and showed that prior RESV treatment protects against neurotoxicity induced by KA (Wang et al., 2004). In this study, a group of rats was concurrently treated with KA (8 mg/kg; once daily for 5 days) and RESV (30 mg/kg; once daily for 5 days) and another group of rats was treated with KA alone (i.e. 8 mg/kg; once daily for 5 days). Animals treated with KA alone displayed significant neurodegeneration, reactive astrocytes and activated microglial cells in the hippocampal CA1 and CA3 subfields and the dentate hilus. In contrast, animals treated with KA and RESV exhibited milder hippocampal neurodegeneration with reduced density of reactive astrocytes and activated microglial cells. Collectively, the above studies suggest the promise of RESV treatment (commencing either prior to or at the time of the excitotoxic injury) for minimizing the excitotoxin-induced seizures, oxidative stress and hippocampal neurodegeneration.

4.2. Potential mechanisms of RESV-mediated neuroprotection against acute seizures

Neuroprotective effects of RESV are likely mediated through multiple mechanisms, which might include the inhibition of the: (i) voltage-gated potassium currents (Gao & Hu, 2005); (ii) electrical activity of CA1 neurons (Li et al., 2005); and (iii) excitatory synaptic transmission in the hippocampus via inhibition of the post-synaptic glutamate receptors (Gao & Hu, 2005). Another study shows that RESV-mediated attenuation of neuronal cell death against SE was associated with suppression of activated astrocytes and microglia (Wang et al., 2004). As increased oxidative stress is a key factor in the mechanisms of KA-induced neurotoxicity, the neuroprotective effect afforded by RESV supports the purported ability of the RESV to act as free radical scavenger to protect against neuronal damage caused by excitotoxic insults. RESV is also capable of both scavenging the superoxide anion generated from rat forebrain mitochondria and decreasing complex III activity, suggesting

that RESV can both scavenge and oppose the production of reactive oxygen species (Zini et al., 1999; See Fig. 1). Several cell culture studies, in addition, demonstrate robust anti-apoptotic properties of RESV (Sun et al., 1997; Nicolini et al., 2001). The anti-apoptotic properties of RESV could involve the regulation of apoptosis-related genes such as Bax, Bcl-2 and caspase-3. Overall, it is likely that RESV-mediated neuroprotection against acute seizures involves anti-convulsant, anti-oxidant, and anti-apoptotic mechanisms. However, additional rigorous studies are required in future to confirm the above possibilities.

4.3. Effects of RESV treatment on SE-induced epileptogenesis and chronic epilepsy

A recent study analyzed the effects of intragastric administration of RESV (15 mg/kg) for 10 days following an intrahippocampal injection of 1.0 µg of KA into anesthetized rats (Wu et al., 2009). Analyses of behavioral spontaneous seizures at an early time-point (8 weeks) after KA injection suggested that only a smaller percentage of animals exhibit spontaneous seizures among rats receiving both KA and RESV, in comparison to rats receiving KA alone. Furthermore, EEG recordings for a brief period of 2 h suggested that epileptiform-like waves were reduced in rats receiving both KA and RESV, in comparison to rats receiving KA alone. Histological analyses revealed considerable neuroprotection in the CA1 cell layer and CA3a sub region in the KA plus RESV treated rats, in comparison to a widespread neurodegeneration observed in rats receiving KA alone. However, the above regimen of RESV treatment was unable to protect neurons in the CA3b and CA3c sub regions. The synaptic reorganization of dentate mossy fibers (in the form of aberrant mossy fiber sprouting into the inner molecular layer of the dentate gyrus) was also reduced when examined at ~8 weeks after KA injection. The KA plus RESV treated animals also exhibited reduced expression of kainate receptors than rats treated with KA alone.

The above observations support the promise of RESV treatment commencing after the hippocampal injury or acute seizures for reducing the incidence/intensity of injury or acute seizure induced chronic TLE. However, there are quite a few limitations in the above study. First, as KA was administered directly into the hippocampus under anesthesia, acute seizures were minimal in this model and RESV administration did not prevent the direct KA-induced neurodegeneration in the dentate hilus and CA3b and CA3c sub regions. For promotion of RESV as a neuroprotective agent against acute seizures, it will be essential to demonstrate that the administration of RESV commencing after the onset of acute seizures (such as in SE models) offers significant neuroprotection. Second, analyses of various parameters of epileptogenesis were performed at an early time-point after KA injection. This is a major limitation because spontaneous seizures develop progressively and typically require ~4–6 months of time after KA administration to exhibit the full range of seizures (Rao et al., 2006, 2007; Waldau et al., 2010) and seizures sometimes occur in clusters.

4.4. Studies needed to authenticate the efficacy of RESV for treating SE/epilepsy

To authenticate the efficacy of RESV for neuroprotection against acute seizures or SE, rigorous analyses of spontaneous recurrent seizures using chronic EEG recordings are needed at extended time-points (e.g. 4–6 months) after an initial precipitating injury (such as SE) and RESV treatment. Such studies need to validate the potential efficacy of this compound for preventing or greatly diminishing the SE-induced multiple changes (as depicted in Fig. 10). Particularly, its ability for long-term suppression of the SE-induced changes that contribute to epileptogenesis will need to be unraveled. These include the: (i) loss of both principal and GABA-ergic neurons (neurodegeneration) in the hippocampus and the extrahippocampal regions such as the piriform cortex, entorhinal cortex, thalamus and amygdala; (ii) abnormal behavior of newly generated neurons in the DG (aberrant neurogenesis); (iii) abnormal synaptic reorganization (such as the aberrant sprouting of dentate mossy fibers and neosynaptogenesis); (iv) chronic epilepsy development typified by

spontaneous recurrent seizures; and (v) cognitive dysfunction (Fig. 10). The other important questions to address include the following. (1) Does preservation of hippocampal principal neurons and GABA-ergic interneurons through RESV administration after SE prevent abnormal neurogenesis (such as the aberrant migration of newly born neurons)? (2) Does neuroprotection of dentate hilar neurons and CA3 pyramidal neurons through RESV administration after SE prevent the aberrant sprouting and the enhanced excitatory connectivity of dentate mossy fibers? (3) Does the preservation of normal hippocampal cytoarchitecture by RESV after SE (as described above) maintain normal level of neurogenesis at both early and late phases after SE? Furthermore, the much bigger question is, does the overall neuroprotection afforded by RESV against SE prevent the chronic epilepsy development characterized by spontaneous recurrent seizures and cognitive dysfunction? (Fig. 10).

Furthermore, it is critical to identify the window of time after the onset of SE at which RESV provides maximal neuroprotection and prevents the progression of acute seizures into chronic epilepsy and cognitive dysfunction. Moreover, it needs to be determined whether RESV administration during and shortly after SE is sufficient or RESV treatment for a longer period after SE is required for a durable neuroprotection of the hippocampal and extrahippocampal regions. Additionally, the efficacy of RESV treatment for restraining epilepsy and cognitive dysfunction needs to be examined at different phases after SE, such as after: (i) the initial neurodegeneration and inflammatory reaction; (ii) the onset of various epileptogenic changes; and (iii) the commencement of spontaneous seizures (Fig. 11). Because of the anticonvulsant properties of RESV (Fig. 1), RESV administration in chronic epileptic conditions may suppress spontaneous recurrent seizures. Besides, RESV treatment in chronic epileptic conditions may also decrease inflammation and oxidative stress, improve neurogenesis, and ease cognitive dysfunction. These beneficial effects might also involve the activation of SIRT1, AMPK or MAPKs (Fig. 1).

5. Bioavailability and toxicity issues pertaining to RESV

5.1. Bioavailability of RESV

For short-term therapeutic interventions such as after SE, administration of RESV via intraperitoneal, intramuscular or subcutaneous injections appears to be ideal. However, if RESV treatment for SE or brain injury needs to be continued for several weeks or months after SE, then, oral administration will be the most feasible route. Therefore, it is important to know the bioavailability of RESV after an oral administration (Cottart et al., 2010). Pharmacokinetic studies measuring the plasma concentration after an oral intake of RESV in humans suggest the following. When RESV was administered orally at a dose of ~25 mg, the plasma concentration of the free form of RESV ranged from 1 to 5 ng/ml. When a higher dose (5 g, ~equivalent to a dose of 71 mg/kg bw) of RESV was administered, the plasma concentration of the free form of RESV reached 530 ng/ml (Boocock et al., 2007a). The maximum peak plasma concentration was attained in the first 30 min after a low dose intake, whereas intake of a higher dose of RESV delayed the peak plasma concentration to 1.5–2 h after the intake (Cottart et al., 2010). In another study, by administering a single dose of RESV ranging from 0.5 to 5 g, Boocock et al. (2007a) confirmed that the free RESV is absorbed rapidly (peak plasma concentration at 0.83–1.5 h after ingestion) at a relatively low mean plasma concentration (from 73 ng/ml to 539 ng/ml for a 0.5 and 5 g RESV intake respectively). A light rebound was observed after 5–6 h after the administration supporting the occurrence of the enterohepatic cycle (Boocock et al., 2007a; Cottart et al., 2010). Interestingly, the corresponding concentrations of the main metabolites of RESV (resveratrol-3-O-sulfate and monoglucuronides) surpassed those of free RESV by ~20-folds. Furthermore, the plasma half-lives of RESV and its main conjugates were similar (between 2.9 and 11.5 h). In the urine, within 24 h after the administration, excretion rates peaked

during the initial 4-hour collection period. Traces of RESV metabolites were detected in the feces, which is consistent with the enterohepatic recirculation. This study showed that even with a high-dose trans-RESV administration, only a small amount of the free form is present in the plasma. However, it has been suggested that RESV concentrations are probably underestimated in this study as the efficiency of extraction in plasma and urine is ~60–70% (Boocock et al., 2007b).

Overall, from the available studies, it emerges that RESV is well tolerated even at higher doses. It is rapidly absorbed and metabolized mainly as sulfo- and glucuro-conjugates, which are excreted in the urine (Cottart et al., 2010). As the concentrations of free RESV detected in various studies are low in the plasma, one can argue that the overall bioavailability of free RESV is low after an oral administration. However, Cottart et al. (2010) point out several valid issues that need to be considered while evaluating the low bioavailability of RESV. First, when assessing the plasma RESV concentrations, the bound part is not taken into account. This is an important issue because RESV is highly lipophilic (is bound by LDL and albumin). Second, conjugated metabolites may also have RESV-like biological activity. Third, it is possible that a large part of the molecule is bound by cell membranes or lipophilic tissue. From this point of view, free RESV levels in serum are underestimated because of large amounts potentially contained in the cellular fraction. Considering these, the effects of RESV may not be due to the amount of visible plasma fraction of RESV but rather due to RESV cellular fractions that were not quantified (Cottart et al., 2010).

5.2. Potential toxicity of RESV

If RESV is to be used long-term for treating SE or epilepsy, it is important to assess the potential toxicity of RESV. A study by Crowell et al. (2004) examined the effects of administration of 0.3, 1 and 3 g/kg/day trans-RESV for 4 weeks in rats (which is equivalent to 21, 70, and 210 g/day respectively in a human weighing 70 kg; (Cottart et al., 2010)). Only two of the 40 rats receiving the highest dose (3 g/kg/day) died due to nephrotoxicity. However, no adverse event was observed in animals treated with 300 mg/kg/day for 4 weeks. In another study, Williams et al. (2009), using both low and high doses of RESV (up to 750 mg/kg/day for 3 months in rabbits and rats) reported that RESV is well tolerated and non-toxic, has no embryo/fetal toxicity, and has no effect on the reproductive capacity of both male and female rats. In humans, 5 g/70 kg (~71 mg/kg bw) did not result in any adverse event (Cottart et al., 2010). Thus, relatively higher doses of RESV intake appear to be safe based on toxicity assays in RESV-treated animals.

6. Conclusions

Analyses of the efficacy of compounds that have a promise for affording robust hippocampal neuroprotection when administered after the onset of SE, acute seizures or head injury have immense value. This is because robust hippocampal neuroprotection might prevent the acute seizure/injury induced learning and memory impairments and chronic epilepsy development. From a clinical standpoint, such interventions will be highly beneficial for patients who are susceptible to develop chronic TLE after an initial precipitating event such as severe head trauma, acute seizures or SE. From the above discussion, it appears that RESV has a promise as a therapeutic drug for easing injury or acute seizure-induced chronic epilepsy development and cognitive impairments. Nevertheless, to validate the efficacy of RESV, rigorous long-term studies are needed in acute seizure or SE models that evolve into chronic epilepsy with time. Clinical application of RESV can be easily promoted for SE, head trauma and stroke, if RESV treatment after SE or brain injury shows efficacy for greatly diminishing epileptogenesis, cognitive impairments and chronic epilepsy occurrence in animal models. The translational potential

is very high for RESV because administration of RESV was shown to be safe in a pharmacokinetic phase 1 study (Boocock et al., 2007a). Furthermore, studies in humans using RESV to prevent cancer, to treat colon and colorectal cancer, metabolic disease and Alzheimer's disease are currently underway (Marques et al., 2009); <http://clinicaltrials.gov/ct2/results?term=resveratrol>). Additionally, RESV is considered as a food supplement, and a large number of people are already taking RESV as a dietary supplement and higher doses of RESV intake appear to be safe based on toxicity assays conducted so far.

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Abbreviations

AED	Antiepileptic drug
AMP	5' AMP-activated protein
AMPK	5' AMP-activated protein kinase
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic adenosine monophosphate
CA1	Cornu ammonis 1
CA3	Cornu ammonis 3
CREB	cAMP response element binding protein
DG	Dentate gyrus
DNA	Deoxyribonucleic acid
DSGL	Dentate supragranular layer
EEG	Electroencephalographic
ERK1	Extracellular signal-regulated kinase 1
ERK2	Extracellular signal-regulated kinase 2
FeCl3	Ferric chloride
FGF-2	Fibroblast growth factor-2
FOXO3	Forkhead boxO3
GABA	Gamma-amino butyric acid
HDAC	Histone deacetylase
KA	Kainic acid
iNOS	Induced nitric oxide synthase
LDL	Low-density lipoprotein
L-NAME	L-NG-Nitroarginine methyl ester

LPS	Lipopolysaccharide
MAP	Mitogen activated protein
MAPK	Mitogen activated protein kinase
MDA	Malondialdehyde
miR	Micro-RNA
MFS	Mossy fiber sprouting
NMDA	N-methyl d-aspartate
NSC	Neural stem cell
NF-kB	Nuclear factor kappa B
NO	Nitric oxide
p53	Protein 53
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
RESV	Resveratrol
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SE	Status epilepticus
SGZ	Subgranular zone
SIR2	Silent Information Regulator 2
SIRT1	Sirtuin 1 (Silent mating type information regulation 2 homolog 1)
TLE	Temporal lobe epilepsy
TNF-α	Tumor necrosis factor-alpha

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Fig. 1.

The various beneficial effects of resveratrol (RESV) on the normal brain function that provide a strong rationale for administering RESV in conditions such as status epilepticus (SE) or brain injury as a neuroprotective compound. The neuroprotective properties of RESV are supported by its ability to inhibit the lipid peroxidation, reduce brain malondialdehyde levels, enhance the concentration of brain superoxide dismutase, and induce heme oxygenase activity (see the lower right region of the illustration). The role of RESV in the maintenance of mitochondrial function is indicated by its ability to decrease complex III activity, scavenge superoxide anions, inhibit the release of cytochrome C, and block adenosine triphosphate (ATP) generation (see the lower left region). The anticonvulsant properties of RESV are typified by its ability to increase 5' AMP-activated protein kinase (AMPK) activity, reduce spontaneous neuronal discharges, decrease the field excitatory post-synaptic potentials, and decrease the epileptiform discharges following excitation (see the upper left region). The contribution of RESV towards the maintenance of cognitive function is supported by its ability to stimulate AMPK activity, phosphorylate mitogen-activated protein (MAP) kinases, stimulate the neurite outgrowth, and promote neural plasticity and mitochondrial biogenesis (see the upper right region).

Fig. 2.

The structure of the hippocampus at 4 days after status epilepticus (SE) when visualized with the neuron-specific nuclear antigen (NeuN) immunostaining. **A1** and **A3** show anterior and posterior regions of the hippocampus from a vehicle-treated control rat. **B1** and **B3** show anterior and posterior regions of the hippocampus from a KA-treated rat showing moderate hippocampal injury. **C1** and **C3** show hippocampal regions from a KA treated rat showing massive hippocampal injury. **A2**, **B2** and **C2** are magnified views of dentate hilar (DH) regions from **A1**, **B1** and **C1**. Note that, in the moderate injury group (**B1–B3**), the loss of neurons is considerable in the dentate hilus (DH) and the CA1 subfield but modest in the CA3 region. In contrast, in the massive injury group (**C1–C3**), the loss of CA1 and CA3 pyramidal neurons is dramatic throughout the hippocampus. DG, dentate gyrus. Scale bar, **A1**, **B1**, **C1** and **A3**, **B3** and **C3**=500 μ m; **A2**, **B2** and **C2**=100 μ m. The bar chart (**D**) depicts the absolute number of surviving neurons in different regions of the hippocampus of vehicle-treated rats, and KA-treated rats with moderate or massive hippocampal injury at 4 days post-administration. The loss of neurons in KA treated rats with moderate hippocampal injury is significant in the dentate hilus, and CA1 and CA3 pyramidal cell layers. However, there is no loss of neurons in the granule cell layer. The massive injury group exhibits greater loss of CA1 and CA3 pyramidal neurons than the moderate injury group. Moreover, the dentate gyrus of the massive injury group exhibits significant loss of both dentate granule cells and dentate hilar neurons. DH, dentate hilus; GCL, granule cell layer.

Fig. 3.

The extent of inflammation in the hippocampus after an episode of status epilepticus (SE) when visualized with the immunostaining for ED-1 antigen (a trans-membrane protein that identifies activated microglial cells). Figure **A1** illustrates a higher density of activated microglia in regions of the neurodegeneration such as the dentate hilus (DH) and the CA1 subfield. **A2** is magnified view of activated microglia from a region of the DH. For ED-1 immunostaining methods, see Hattiangady et al. (2011). Scale bar, **A1**=500 μm ; **A2**=100 μm .

Fig. 4.

Status epilepticus impairs the ability for spatial learning and spatial memory retrieval even at extended time-points after an episode of SE. The figure A on the left side compares the spatial learning ability of rats that underwent SE and developed chronic epilepsy at ~4-months after SE (indicated by a red line) with the age-matched naive rats (indicated by a green line) in a water maze test (WMT). Note that, in comparison to intact rats, the average swim path lengths to reach the platform were much greater in rats exhibiting chronic epilepsy in all of the eleven training sessions (A). Naïve rats learn quickly to locate the hidden platform using spatial cues and hence their swim path lengths are much shorter after 3–4 sessions of learning. The epileptic rats are clearly slow learners and exhibit overnight forgetting. The figures in B and C show the results of a probe test (i.e. a 30 second memory retrieval test for each rat without the hidden platform) conducted one-day after the eleven learning sessions performed over 6 days. The circular diagram on the left side of figure B depicts the various water maze tank quadrants in different colors and the swim path of a naïve rat. Note that this naïve rat exhibits robust memory retention, as it swam straight to the quadrant where the platform was originally placed (gray-colored area) and spent most of its probe test time searching for the platform in this quadrant. The circular diagram on the right side of figure B illustrates the swim path of a chronically epileptic rat in various quadrants of the water maze tank. Note that this epileptic rat explored all quadrants of the maze without any specific affinity for the quadrant where the platform was originally placed. The bar chart in C compares the dwell time of rats from the naïve group and the epileptic group in different quadrants of the water maze tank. Note that control rats spend most of their probe test time in the platform quadrant (gray colored bar) whereas epileptic rats spend more or less equal amount of time in all four quadrants, clearly implying that chronically epileptic rats exhibit memory dysfunction. For methods pertaining to water maze tests, see Hattiangady et al. (2011).

Fig. 5.

Changes in the dentate neurogenesis after an episode of status epilepticus (SE) induced by kainic acid. Newly born neurons in the dentate gyrus (DG) of a naïve adult rat (**A1**) and an adult rat that underwent status epilepticus 12 days prior to euthanasia (**B1**) were visualized with immunostaining for doublecortin (a marker of newly born neurons). **A2** and **B2** show magnified views of regions of dentate gyrus from **A1** and **B1** respectively. Note that, in comparison to the dentate gyrus of a control rat (**A1**, **A2**), a rat that underwent SE (**B1**, **B2**) exhibits considerably increased density of doublecortin + new neurons and abnormal migration of newly born neurons into the dentate hilus (indicated by arrowheads in **B1**). **C1** is magnified view of a region from **B1** showing aberrantly migrated newly born neurons in the dentate hilus. DH, dentate hilus; GCL, granule cell layer; SGZ, subgranular zone. Scale bar, **A1** and **B1**=200 μ m; **A2**, **B2** and **C1**=50 μ m.

Fig. 6.

Status of dentate neurogenesis in chronic epilepsy as revealed by doublecortin (DCX) immunostaining. **A1–C1** illustrate the distribution of DCX positive newly born neurons in the dentate gyrus of an age-matched intact rat (**A1**), a rat exhibiting chronic epilepsy at 5 months after an intracerebroventricular (ICV) kainic acid (KA) administration (**B1**), and a rat displaying robust chronic epilepsy at 5-months after intraperitoneal (IP) KA-induced status epilepticus (SE) (**C1**). Note that, in comparison to the age-matched intact hippocampus, hippocampi from chronically epileptic animals exhibit dramatically reduced density of DCX positive newly generated neurons. Arrowheads point to regions in the subgranular zone (SGZ) where neurogenesis is active. The arrow in **C1** denotes a neuron that has migrated into the dentate hilus. **A2**, **B2**, and **C2** are magnified views of regions from **A1**, **B1**, and **C1** demonstrating the morphology newly generated neurons in the three groups. In the dentate gyrus of the age-matched intact rat (**A2**), DCX positive new neurons exhibit long apical dendrites that extend into the molecular layer (ML) through the granule cell layer (GCL). Contrastingly, in hippocampi from epileptic animals (**B2**, **C2**), a vast majority of DCX positive neurons display basal dendrites (indicated by short arrows). The bar chart compares the absolute numbers of DCX positive new neurons in different groups. Note that, in comparison to the age-matched control rats, the overall dentate neurogenesis in hippocampi of chronically epileptic rats is drastically reduced. Furthermore, the decline is more pronounced in the hippocampus of rats exhibiting robust chronic epilepsy (i.e. the hippocampus at 5-months post-SE) than the hippocampus of rats exhibiting fewer spontaneous seizures (i.e. the hippocampus at 5-months post-ICV KA administration). DH, Dentate hilus; GCL, Scale bar, **A1**, **B1**, **C1**=200 μ m; **A2**, **B2**, **C2**=50 μ m.

Fig. 7.

Differentiation of newly born cells into neurons, astrocytes, and oligodendrocyte progenitors at 24 h after twelve daily injections of BrdU in the chronically epileptic hippocampus. Examples of newly born cells that differentiate into doublecortin + (DCX+) immature neuron (**A1–A3**), TuJ-1+ neuron (**B1**; indicated by an arrow), S-100 β + astrocyte (**C1**; denoted by an arrow), and NG2+ oligodendrocyte progenitor (**D1**; showed by an arrow) in the subgranular zone-granule cell layer (SGZ-GCL) are illustrated. Scale bar, **A1–A3**=5 μ m; **B1, C1, D1**=10 μ m. The bar chart in **E1** compares percentages of newly born cells (i.e. BrdU + cells) that express DCX, TuJ-1, S-100 β or NG2 in the subgranular zone-granule cell layer (SGZ-GCL) between the age-matched intact hippocampus and the chronically epileptic hippocampus. Note that the neuronal differentiation of newly born cells is dramatically decreased but differentiation of newly added cells into S-100 β + or NG2+ glia is considerably enhanced in the chronically epileptic hippocampus.

Fig. 8.

The upper panel shows that, status epilepticus (SE) depletes the population of GABA-ergic interneurons expressing the neuropeptide, the neuropeptide Y (NPY). Figure **A** illustrates the distribution and density of NPY immunopositive interneurons in the dentate hilus of a naïve rat. Figure **B** shows the distribution and density of NPY + interneurons in the dentate hilus of an age-matched rat that underwent kainic acid induced SE and acquired chronic epilepsy. Note that the overall density of NPY + interneurons is greatly reduced after SE. For NPY immunostaining methods see Rao et al. (2006). Scale bar, **A1** and **A2**=200 μ m. The lower panel illustrates the extent of the aberrant mossy fiber sprouting in rats with moderate hippocampal injury (**B1–B2**) and rats with severe hippocampal injury (**C1–C2**), in comparison to age-matched intact rats (**A1–A2**), visualized by Timm's histochemical staining. Note that, in comparison to rats exhibiting moderate hippocampal injury (**B1–B2**), the rats showing severe hippocampal injury (**C1–C2**) have much robust aberrant sprouting of mossy fibers into the dentate supragranular layer (DSGL). Asterisks in **C1** denote mossy fiber sprouting in the DSGL. DH, dentate hilus; GCL, granule cell layer. Scale bar, **A1**, **B1** & **C1**=500 μ m; **A2**, **B2** and **C2**=200 μ m.

Fig. 9.

Electrical activity in the hippocampus during a spontaneous seizure in a chronically epileptic rat, as recorded through electroencephalography (EEG). The activity was recorded through an electrode implanted into the dentate gyrus. Note the presence of persistent large amplitude and high frequency polyspikes for over 50 s. Polyspikes represent a complex paroxysmal EEG pattern with close association of two or more diphasic spikes occurring more or less rhythmically in bursts of variable duration, generally with large amplitudes. For methods of electrode implantation into the dentate gyrus, see Rao et al. (2006).

POTENTIAL OUTCOME OF RESVERATROL THERAPY FOR SE & EPILEPSY

Fig. 10.

Potential outcome of resveratrol (RESV) therapy for status epilepticus (SE) and epilepsy. The overall outcome of RESV treatment would likely depend on the time-point of its administration after an initial precipitating injury (IPI) such as SE or head injury. An IPI such as SE leads first to changes that comprise increased excitation of neurons, enhanced oxidative stress, considerable neurodegeneration, inflammatory reaction and abnormal neurogenesis, which are broadly classified as “early changes”. While most of these changes can occur in several brain regions, the hippocampus has been recognized as the most vulnerable region to SE for exhibiting all of these changes. This initial phase is typically followed by an intermediate “epileptogenesis” phase during which the various epileptogenic changes occur. These include the loss of GABA-ergic interneurons, decreases in the functional inhibition, aberrant sprouting of axons, and abnormal integration of newly born neurons. All of these changes are believed to contribute towards the development of an epileptogenic circuitry, which gradually leads to a state of “chronic epilepsy” typified by spontaneous recurrent seizures, decreased hippocampal neurogenesis and cognitive dysfunction. Considering the above, the commencement of RESV treatment immediately after the induction of SE may either prevent or greatly minimize the early changes, which may block “epileptogenesis” as well as the evolution of SE into “chronic epilepsy”. This hypothesis is based on the anticonvulsant, anti-oxidant, anti-inflammatory, and anti-apoptotic properties of RESV. On the other hand, the commencement of RESV treatment after “early changes” may reduce the extent of “epileptogenesis” through preservation of greater numbers of GABA-ergic interneurons, dampening of hippocampal hyperexcitability and maintenance of normal neurogenesis. These actions of RESV may considerably restrain the development/intensity of chronic epilepsy and cognitive dysfunction. This premise is based on the neuroprotective, anti-inflammatory and anticonvulsant properties of RESV. Furthermore, the commencement of RESV treatment after most of the epileptogenic changes occurs or after the establishment of a chronic epileptic state may still restrain the intensity of chronic epilepsy and improve the cognitive function. This proposition is based on the anti-inflammatory and anticonvulsant properties of RESV and the ability of RESV to activate SIRT1.