What is new for an old Molecule? Systematic Review and Recommendations on the use of Resveratrol

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Supporting information:

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| **Table S4:** Neuroprotective effect of resveratrol (acute, sub chronic and chronic exposure) |
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| **Animal** | **Treatment** | **Resveratrol dose** | **Duration** | **Effect** | **References** |
| Acute models |
| Wistar male rats | Weight-drop method was used for achieving head trauma | 100 mg/ kg bw, single dose of Resv | Acute exposure | Tissue lesion area ↓ | [1] |
| Wistar male rats | Weight-drop trauma modeling | 100 mg Resv/ kg bw,ip immediately after trauma | Acute exposure | Recovery of impaired motor function score ↑Recovery of impaired inclined plane score ↑Spinal cord injury area ↓ | [2] |
| Long-Evans rats | Focal cerebral ischemia induced by occlusion of the middle cerebral artery (MCA) for 1 hour | 0.1 and 1 µg Resv/ kg bw was iv injected after 1 hour MCA occlusion | Acute exposure | Infarct volume ↓ by 1 µg/kg Resv | [3] |
| Sprague–Dawley male rats | Right middle cerebralartery occlusion (MCAO) | Systemic inject. of Resv ( 2x10-3, 2x10-4, 1x10-4mg/ kg bw) | Acute exposure | Infarct area ↓MCAO induced renal sympathetic nerve activity ↓ | [4] |
| Wistar male rats | Middle cerebral artery occlusion (MCAO) | 100 mg Resv/kg bw administrated iv, 15 min before occlusion and the time of reperfusion  | Acute exposure | MCAO-induced brain edema↓MCAO-induced cerebral ischemia ↓ | [5] |
| Wistar male rats | Cerebral ischemia induced by bilateral cerebral artery ligation | iv: 20 mg Resv/ kg bw | Single exposure | Ischemia induced neuronal damage scorea in hippocampus ↓Ischemia induced SOD ↓NO ↑ | [6] |
| Sprague–Dawley rats | Asphyxial cardiac arrest (ACA) | ip: 50 or 100 mg Resv/ kg bw 48 h before the induction of ACA | Acute exposure | Tolerance against brain injury ↑ | [7] |
| Male Wistar rats | Kainate-induced epileptic rats (intra-hippocampal injections) | ig: 15 mg Resv/ kg | Acute exposure | Frequency of spontaneous seizures ↓Epileptiform discharges↓counteract kainate-induced neuronal cell death | [8] |
| Sprague-Dawley rats | Spinal cord injured | 50 and 100 mg Resv/ kg bw (ip) immediately after trauma | Acute exposure | Edema-induced cell death ↓Edema-induced lipid peroxidation ↓ | [9] |
| Wistar rats (7-day-old pups) | Percussion traumamodel in immature rats | 100 mg/kg resveratrol (ip) immediately after trauma | Acute exposure | Trauma-induced decreased locomotor activity ↑Trauma-induced decreased memory discrimination index ↑ | [10] |
| Male Swiss mice | Induction of neurotoxicity by 40 mg/ kg bw dose of lindane | 5 mg Resv/kg in combination with other antioxidants50 mg/kg Vitamin C20 mg/kg α-lipoic acid 50 mg/kg Vitamin E | Acute exposure | Lindane-decreased level of AChE in cerebellum and pons-medullaAntioxidants: ↑Lindane-decreased level of butyryl cholinesterase in cerebellum and pons-medullaAntioxidants:↑  | [11] |
| New Zealand rabbits | Spinal cord ischemia - occlusion of the infrarenal aorta | 1 or 10 Resv mg/kg given 30 min before operation | Acute exposure | Paraplegia was significantly counteracted by 20 mg Resv/ kg | [12] |
| Sub chronic / chronic exposure |
| Wistar male rats | Middle cerebral artery occlusion (MCAO) | 20 mg Resv/ kg bw daily (ip) before MCAO | 21 days | MCAO reduced grip score ↑MCAO reduced time on rota rod ↑MCAO reduced locomotor activity ↑MCAO induced lipid peroxidation ↓MCAO induced GSH ↓MCAO infarct volume ↓ | [13] |
| Sprague-Dawley male rats | Controlled cortical impact (CCI) model | 100 mg Resv /kg bw (ip) |  3 days | Motor performance ↑Visuospatial memory ↑ | [14] |
| Sprague–Dawley male rats | Middle cerebral artery occlusion (MCAO) | 30 mg Resv /kg bw (ip)  | 7 days | MCAO induced infarct ↓MCAO induced neurological deficit ↓ | [15] |
| Sprague Dawley male rats | Kainic acid (8 mg/kg bw) daily for 5 days caused neuronal death and activation of astrocytes and microglial cells  | 30 mg Resv/kg bw/day | 5 days | Neuronal death ↓Activation of astrocytes ↓ Activation of microglial cells ↓ | [16] |
| Sprague–Dawley rats | Injection of 6-hydroxy-dopamine (6-OHDA) into the right striatum | 10, 20 or 40 mg Resv/ kg bw/ day (po) | 10 weeks | 6-OHDA-induced contra lateral turns ↓ | [17] |
| Wistar male rats | Injection of 10 μg 6-OHDA (ig) | Daily injection with 20 mg Resv/ kg bw (ip) | 15 days | 6-OHDA-induced contralateral rotations ↓6-OHDA-depleted muscles coordination ↑6-OHDA-impairment in the adjusting steps ↑ | [18] |
| Sprague–Dawley male rats | Daily i.p. injection with 10 mg/kg 3-nitropropionic acid (3-NPA) | Daily ip injection with 100 mg Resv/ kg | 4 weeks | 3-NPA-induced paresis ↓3-NPA-reduced motor nerve conductivity ↑ | [19] |
| Wistar male rats | ip administration of NPA (20 mg/kg bw for 4 days) | 5 or 10 mg Resv/ kg bw, po, from day 4 before injection of NPA | 8 days | 3NPA- induced motor impairment ↓3NPA- induced cognitive impairment ↓ | [20] |
| Sprague–Dawley male rats | 55 mg STZ/ kg bw(ip) | Daily 10 or 20 mg Resv/ kg bw  | 2 weeks | Diabetes induced motor conduction velocity (MCV) ↑ | [21] |
| Sprague–Dawley male rats | 55 mg STZ/ kg bw(ip) | Daily 10 mg Resv/ kg bw | 2 weeks | Diabetes reduced MCV ↑Diabetes reduced nerve blood flow ↑ | [22] |
| Wistar male rats | 60 mg STZ/ kg bw(ip) | Daily 10 mg Resv/ kg bw (ip) | 6 weeks | In regions of the central nervous system:STZ-reduced GSH ↑STZ-induced lipid peroxidation ↓ | [23] |
| Wistar male rats | 55 mg STZ/ kg bw (ip) | Daily 10 or 20 mg Resv/ kg bw (po) | 30 days | STZ-induced AChE activity in cerebral cortex synaptosomes ↓ | [24] |
| Wistar male rats | Intracerebroventricular administration of colchicine (15 μg) | 10 and 20 mg Resv/ kg bw (po) beginning 4 days prior to colchicine injection | 25 days | Colchicine-induced cognitive impairment ↑ | [25] |
| Wistar rats | Induction of vasospasm: autologous blood (0.3 mL) was injected into the cisterna magna.  | iv injection of 10 mg Resv/ kg bw/ day | 3 days | Relaxation of smooth muscle in the wall of the basilar artery ↑Neuroprotection against cerebral ischemia ↑ | [26] |
| Wistar male rats |  | Daily 1.25 – 25 mg Resv/ kg bw (ip) | 7 days | Lipid peroxidation in brain ↓Antioxidative enzymes ↑ | [27] |
| p25-CK transgenic mice on a C57BL6 background |   | Intra cerebro ventricular injection (2.5 µg Resv) every 2-3 day | 3 weeks | Associative learning wasrescued Neurons survival ↑ | [28] |
| Male Balb/c mice | Injury induced by MCA occlusion and reperfusion | 50 mg/kg bw/ day, gavages | 7 days | Mean neurologic scores ↓infarct volumes of the ischemia and reperfusion groups↓ | [29] |
| C57BL/6 mice | Injury induced by MCA occlusion and reperfusion | 20 mg Resv / kg bw/ day | 7 days | MCA-induced infarct volumes ↓ | [30] |
| C57BL/6 mice | 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) targets nigrostriatal dopaminergic neurons | 50 or 100 mg Resv/ kg bw/ day | 1 or 2 weeks | MPTP-induced depletion of striatal dopamine ↑Rescue nigral neurons from MPTP insults ↑ | [31] |
| Male Balb/C mice | MPTP treatment (30 mg/kg, ip) | 20 mg Resv/ kg bw/ day, iv | 7 days | Motor coordination ↑MPTP-induced muscle rigidity ↑ | [32] |
| Male C57BL/6 | MPTP treatment (4 injections of 7 or 10 mg/kg, ip) | 50 mg Resv/ kg/ day, gavage100 mg Resv/ kg/ day, gavage | 7 days /14 days before MPTP | MPTP-reduced striatal dopamine ↑MPTP-reduced striatal tyrosine hydroxylase ↑ | [31] |
| SJL/J mice | Induction of EAE by proteolipid protein peptide | Intravitreal injections of 5, 10 and 80 pmol SRT501 on day 0, 3, 7 and 11. | 2 weeks  | Acute loss of retinal ganglion cell ↑Optic nerve inflammation → | [33] |
| Male C57BL/6 mice | Diabetes induced by 55 mg STZ/ kg bw (ip), once a day for 5 days | 20 mg Resv/ kg/ day by gavages | 4 weeks | STZ induced retinal cell death ↓ | [34] |
| C57BL/6 mice | Standard diet or high fat diet | ~ 200 mg Resv/ kg/ day in diet or by mini pump | 4 weeks | Brain MnSOD level and activity in high fat mice ↑Brain catalase activity →Brain GSH Peroxidase activity in high fat mice ↓ | [35] |
| Offspring of Tg19959 crossed with C57/B6SJL |  | 0.2% Resv in diet (~300 mg/ kg bw/ day) | 45 days | Plaque formation ↓ | [36] |
| ddY Mice | Permanent MCAO  | 20 mg Resv/ kg bw/ day | 3 days | Brain infarct volume ↓ | [37] |
| C57BL/6N female mice | Middle age (12–15-months-old) exposed to 0.76 g EtOH /kg bw) | 1.15 mg Resv/ day in the drinking water (~44 mg/ kg bw + 0.71 g EtOH /kg bw | 6 weeks | Cued learning: : EtOH+Resv relative to EtOH →Spatial learning: EtOH+Resv relative to EtOH ↑ | [38] |
| male C57Bl/6 mice | 24 month age mice | 0.15 mg Resv/ g diet (~ 18 mg/ kg bw), starting when 12 month old | 12 month | Acquisition of a spatial Y-maze test ↑ | [39] |
| ACA: Asphyxial cardiac arrest; AChE: Acetylcholine esterase; EAE: Experimental autoimmune encephalomyelitis; GSH: Reduced glutathione; MCAO: middle cerebral artery occlusion; MCV: motor conduction velocity; 3NPA: 3-nitropropionic acid; MnSOD: Mn-superoxide dismutase; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine; 6-OHDA: 6-hydroxydopamine; STZ: streptozotocin; ig: intra gastrically; iv: intravenous; po: per oral;Effect are indicated by ↓: reduction; ↑: enhancement; →: no effect. |

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