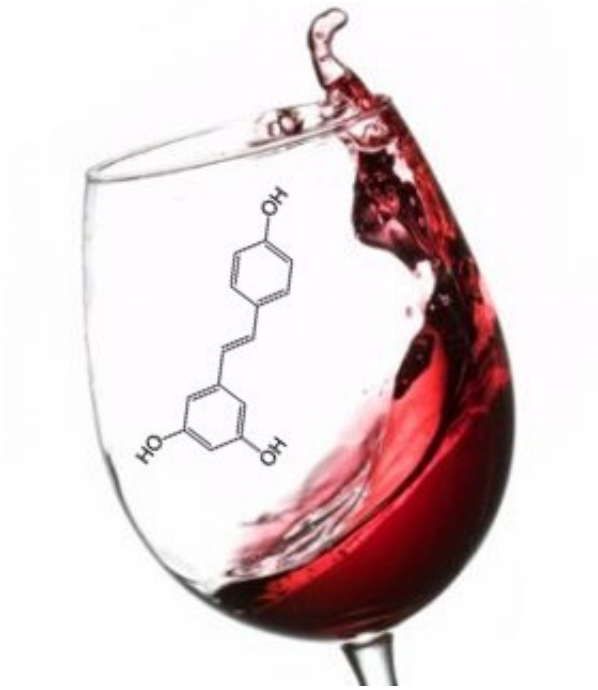
Could red wine improve cognitive performance?

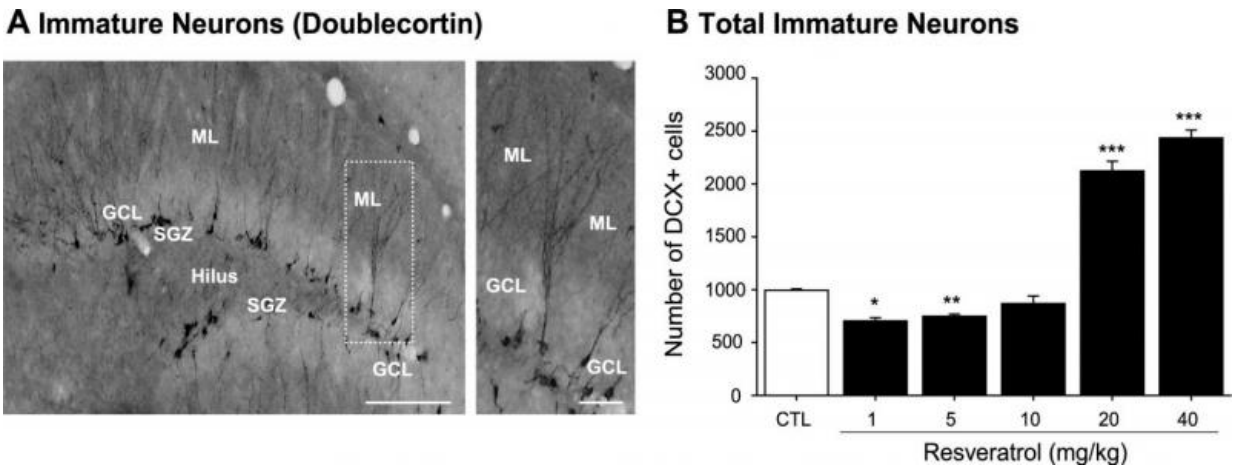
January 12 2016, by Plos Blogs



"Wine is the most healthful and most hygienic of beverages," said Louis Pasteur. Through the biological activity of several classes of organic compounds such as anthocyanins, tannins and flavonoids, red wine is known to have beneficial effects on health, when consumed in moderation. These natural organic compounds, in particular flavonoids, show anti-inflammatory, anti-oxidant and anti-aging properties, thus beneficially affecting health. However, the cellular and molecular

mechanisms underlying the positive effects of flavonoids remain unknown.

In a recent paper published in *PLOS One*, Torres-Perez and colleagues investigated the neurobiological effects of the natural flavonoid found in grapes Resveratrol (RVTL) on hippocampal neuroplasticity and cognitive performance in rodents using a wide range of techniques (Torres-Perez et al., 2015). Although several reports have already highlighted a neuroprotective effect of RVTL (Sonmez et al., 2007; Vingtdeux et al., 2010), its neuroprotective mechanisms have remained elusive. As such, Torres-Perez and coauthors decided to explore the complex beneficial effects of RVTL on the hippocampus, a key brain region involved in aging as well as in learning and memory functions.

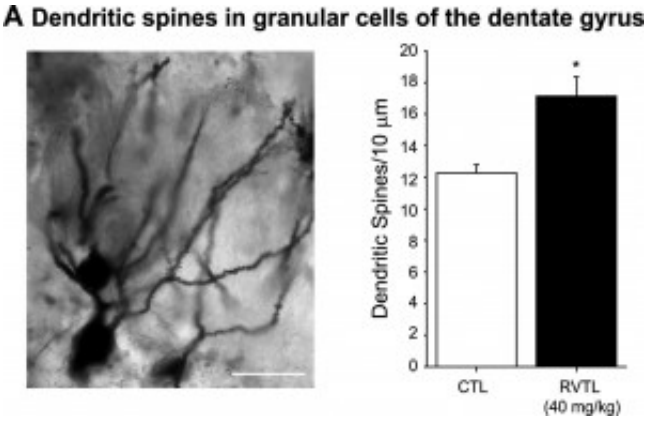


Resveratrol increases the number of immature neurons in the hippocampus

Effect of Resveratrol on cell survival and proliferation

Cell survival and proliferation of hippocampal neurons may counteract

the cognitive decline usually observed during aging; therefore, the primary focus of the authors was on the potential effect of RVTL on these two mechanisms. To this end, hippocampi of 6-month old mice treated for 14 consecutive days with RVTL at different doses (1-40 mg/kg) were analyzed by immunohistochemistry paying particular attention to the dentate gyrus. Based on the expression of cellular markers specific for cell proliferation (Ki67), cell survival (BrdU) and early stage of neuronal development (Doublecortine, DCX), Torres-Perez and colleagues reported that Resveratrol is able to promote cell survival and neurogenesis in the mouse hippocampus.



Resveratrol induces spinogenesis.

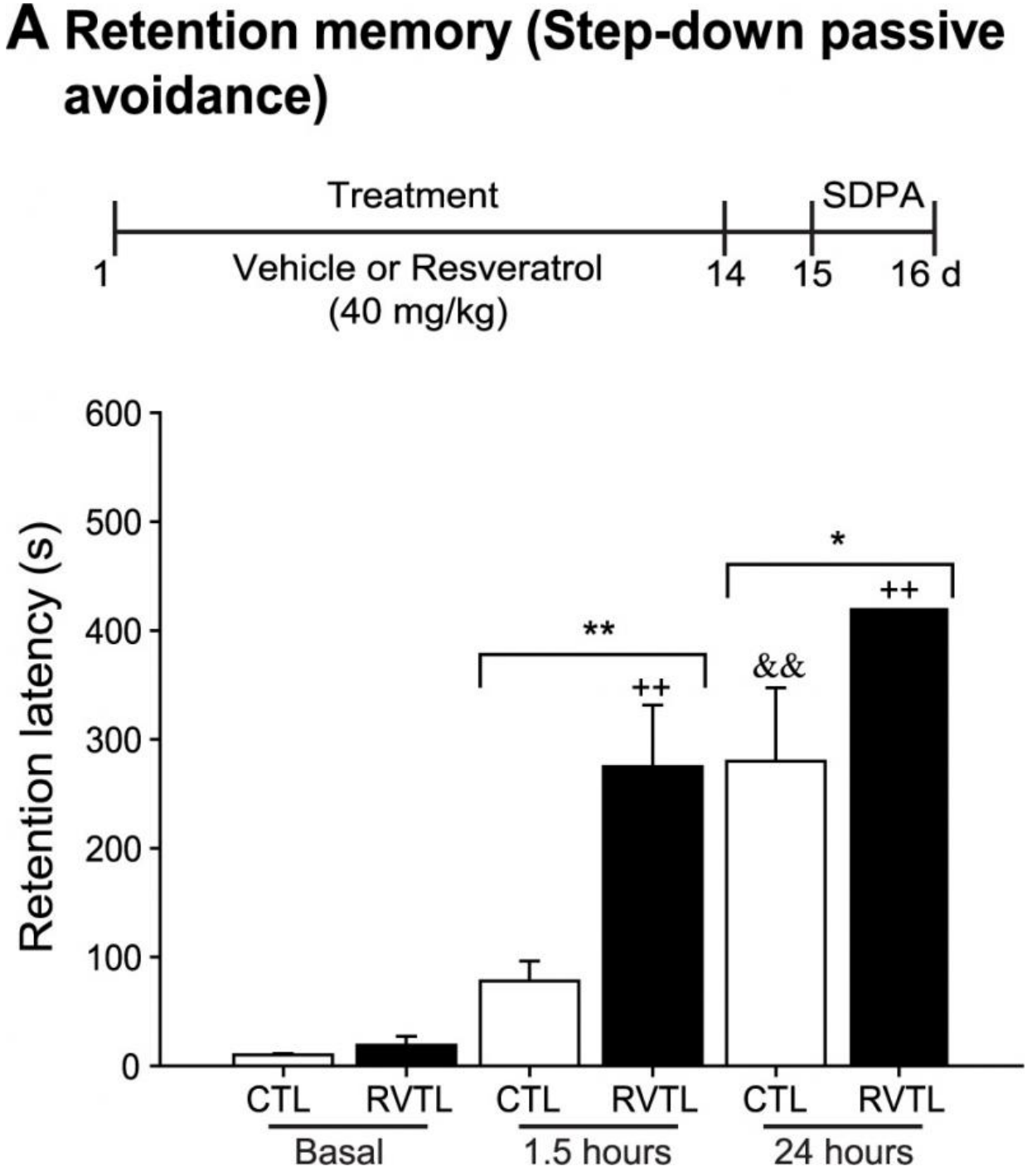
These results indicate that RVTL has an important impact on neuronal plasticity, thus providing evidence of neuroprotective activity. According to the authors, "the survival of new born cells is of central importance, particularly because [their] general hypothesis is that adult hippocampal neurogenesis provides a "neurogenic reserve" that allows for the maintenance of cognitive flexibility in older age." In spite of the relevance of this finding, the authors knew that cell survival itself might not be the only mechanism through which RVTL could act on the brain

and so they explored other alternatives as well.

Effect of resveratrol on neuronal morphology

Neurons are complex elements exhibiting a sophisticated morphology characterized by small boutons (spines) on their dendrites. Dendritic spines assure the flow of information between neurons and among brain structures and are subject to continuous remodeling. It is thought that this structural remodeling is an essential mechanism for learning and memory functions since a reduction in dendritic spine number has been associated with cognitive decline (e.g. Alzheimer's disease).

Consequently, Torres-Perez and coauthors decided to carefully scrutinize the morphology of dendritic spines in RVTL-treated mice. Interestingly, they observed that RVTL was able to increase both the number of dendritic spines and the proportion of mature dendritic boutons, which suggests that RVTL may have a "beneficial effect on the learning and memory processes," according to Dr. Ramirez-Rodriguez, team leader and senior scientist of the study.



Resveratrol improves retention of associative memory in the passive avoidance behavioral test

Effect of resveratrol on memory performance

Whether cell survival and spine formation occurred in parallel with the potential neuroprotective effects of RVTL on associative memory remained unknown. To answer to this critical question, Torres-Perez and colleagues used the step-down passive avoidance (SDPA) method, which is sensitive to associative memory function. The SDPA test is a fear-aggravated model that involves learning to inhibit a response (natural exploratory drive) in order to avoid an aversive stimulus (footshock). The latency to repeat the punished response is considered to be an index of retention memory. Mice treated for 14 days with RVTL showed increased retention latency at both 1.5 hours (short-term) and 24 hours (long-term) after basal test, thus revealing improved cognitive performance. Such amelioration is thought to be specific to associative memories since working and reference memories, evaluated using the 8-radial arm maze test (8-RAM) behavioral paradigm, were not altered. "This finding provides additional evidence to support the hypothesis that RVTL exerts beneficial effects on the brain," said the authors.

Finally, at the cellular and molecular levels, cell survival, spine remodeling and memory formation require the activity of specific cell signaling players such as kinases. Among a plethora of signaling molecules, increased activities of two critical kinases, Akt and PKC, have been reported to correlate with neuroprotective events, as well as to shape neuronal cytoarchitecture. Hence, the authors of the study measured the levels of these two kinases in the hippocampus of RVTL-treated mice. Protein analysis revealed increased levels of activated Akt and PKC following treatment with RVTL, thus indicating that Akt- and PKC-dependent signaling pathways may be involved in the neuroprotective effects triggered by RVTL treatment.

Conclusions

Despite the richness of the findings presented by the authors, a direct and causal link between the observed phenomena and the neuroprotective properties of RVTL is still missing. For example, would inhibition of spine maturation be able to reverse RVTL-induced amelioration of memory performance? Would selective inhibition of Akt and PKC signaling pathways be capable of counteracting the beneficial effects of flavonoid treatment?

Future investigations are required to fully establish a complete and detailed picture of the mechanisms underlying the positive effects of this grape-derived natural compound on brain function. However, one thing is for certain: in a society characterized by an unbalanced life style, stress and fast-food alimentation, a healthy diet is a good move to help improve our brain function. What better place to start than wine—in moderation?

More information: Mario Torres-Pérez et al. Resveratrol Enhances Neuroplastic Changes, Including Hippocampal Neurogenesis, and Memory in Balb/C Mice at Six Months of Age, *PLOS ONE* (2015). DOI: 10.1371/journal.pone.0145687

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