Geroprotectors: Anti-Aging Molecules

Geroprotectors are molecules that have been shown to slow aging and/or extend lifespan in experimental animals. A group of mainly Russian scientists have collaborated on a website that lists all known geroprotectors: anti-aging molecules.

Many compounds are listed on the site, and we've discussed many of them here as well, but we'll just look at a few of them here that have been tested in a couple of recent experiments. They are:

- rapamycin
- metformin
- berberine
- resveratrol
- vitamin D3
- aspirin
- EGCG
- n-acetylcysteine
- caffeine

Screening geroprotectors in cell culture

The first study is Potential anti-aging agents suppress the level of constitutive mTOR- and DNA damage- signaling.

Activation of the mammalian target of rapamycin, or mTOR, is thought to be a very important pro-aging mechanism. It's not surprising that this paper appeared in the journal *Aging*, of which Mikhail Blagosklonny is the editor,

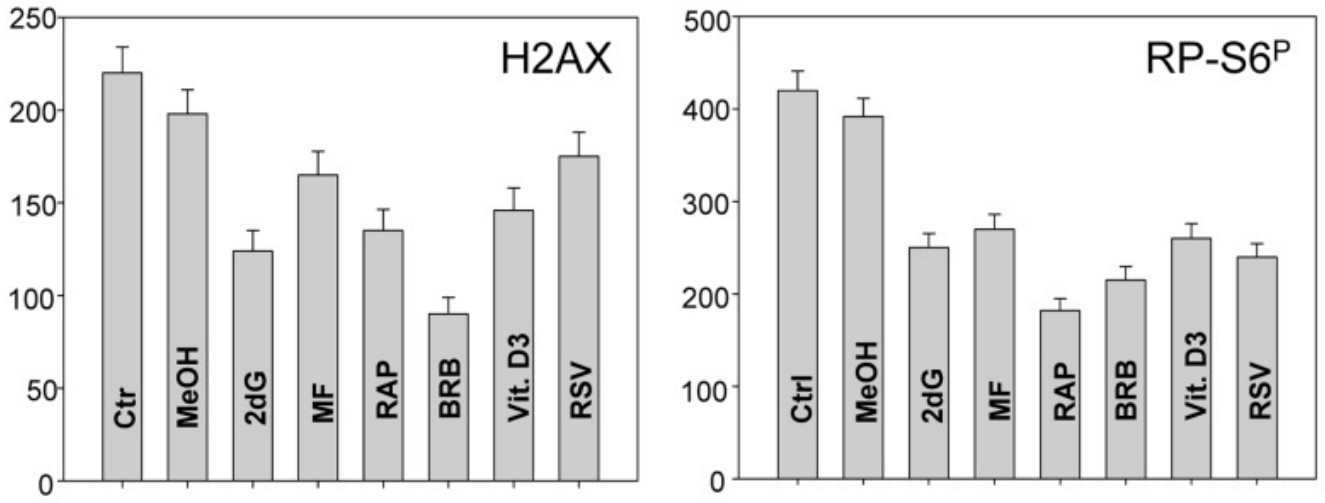
as he's been one of the most prominent proponents of the involvement of constitutive mTOR activation in aging. Rumor has it that he's started taking rapamycin himself.

DNA damage also increases in aging.

Both of these processes, mTOR activation and DNA damage, are decreased by calorie restriction, the potent life-extension intervention.

The scientists who did this research tested the first 6 compounds listed above in cell culture systems to elucidate whether they kept a lid on mTOR activation and DNA damage. A relatively simple system like a cell culture can be used to rapidly screen compounds for potential anti-aging effects. In this case, the compounds tested were all known to extend lifespan in one case of another, so the scientists wanted to see how they worked in cell culture with regard to the two processes.

Below is a chart of how these compounds affected DNA damage, using two different indicators.



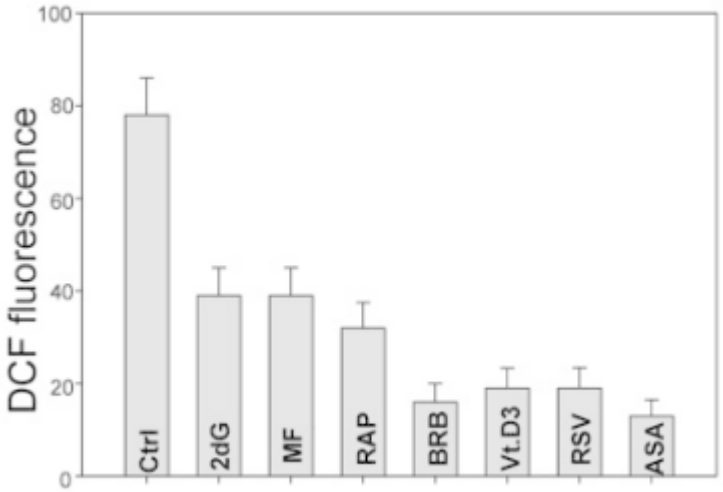
In this system, aspirin is not listed as it had no effect. 2dG is deoxyglucose, a compound that inhibits glucose metabolism and extends lifespan in *C. elegans*, but that is toxic in rodents. 9Which is why I didn't list it above.) All the compounds (except aspirin) were effective, with berberine and rapamycin being among the most effective.

Next, the scientists looked at the ratio of phosphorylated mTOR to mTOR. In this case, lower is better, meaning mTOR is less activated.

Agent	Ctrl	2dG	MF	RAP	BRB	Vit. D3	RSV	ASA
$mTOR^P$	1.00	0.73	0.76	0.89	0.99	0.96	1.51	0.75
m-TOR	1.00	1.45	2.25	1.41	1.04	1.07	3.96	1.44
RATIO	**1.00**	**0.50**	**0.34**	**0.63**	**0.95**	**0.90**	**0.38**	**0.52**

Here, metformin was the winner, followed by resveratrol and aspirin.

They also looked at the levels of reactive oxygen species (ROS), a measure of free radical damage in the cells, compared to control.



Here, aspirin was the clear winner, followed by berberine, resveratrol, and vitamin D.

Another recent study looked at the ability of berberine to suppress the conversion of cells into senescent cells. It did so, through deactivation of mTOR with subsequent lower levels of DNA damage.

Another study attempted to validate known geroprotectors using an in vitro model. The substances that passed were n-acetylcysteine, EGCG (from green tea) and myricetin, a plant flavonoid.

> Each of these three compounds investigated on the pathway level covers a particular side of the senescence process and some of the effects are shared among compounds: EGCG and Myricetin both activate cAMP pathway; Myricetin and NAC inhibit pro-proliferative signaling via MAPK, p38, PAK and AKT signaling, whereas the effect of NAC on these pathways was stronger. The combination of these compounds with proper dosing may reveal synergistic effects and turn out to be even more beneficial than independent use.

Finally, a study, which I discussed in my book Stop the Clock, showed that screening compounds that protected mammalian neurons in culture from glucose toxicity yielded a number that extended lifespan in the worm *C. elegans*. The compounds were caffeine, ciclopirox olamine, tannic acid, acetaminophen, bacitracin, and baicalein. Caffeine is of course well-known; ciclopirox olamine is a known iron chelator and antifungal medication.

Taking geroprotectors

I take some of these compounds myself, as I wrote about recently. From those listed above, I currently take berberine, aspirin, vitamin D3, resveratrol,

EGCG (green tea extract, occasionally), and I drink plenty of caffeine in the form of coffee, tea, and chocolate.

The doses I use are fairly low (except for caffeine), but that's OK, since many of them act via hormesis, that is, low-level toxicity that promotes stress resistance. So you don't need much. That being said, optimal doses of these for humans are unknown for the most part.

The cell culture and in vitro models used in the studies discussed above are very promising ways to test known anti-aging compounds and to screen for others. They allow researchers a much cheaper and faster way to test many compounds without a long, expensive experiment using many animals. These methods also show what these compounds are doing physiologically, elucidating their mechanisms of action.