A spoonful of sugar

Mary Poppins may not be medically trained, but she was right about at least one thing: a spoonful of sugar really does help the medicine go down. Mannitol is a sugar alcohol used commercially as an artificial sweetener and medically to facilitate the delivery of drugs into the brain by disrupting the blood–brain barrier. Now, scientists at Tel Aviv University (Israel) and University of California San Diego report that it also disrupts the aggregation of the protein α-synuclein in the brain, a process characteristic of Parkinson's disease. The discovery may lead to new therapies for Parkinson's and other neurodegenerative diseases.

After identifying mannitol as an effective compound for inhibiting α-synuclein aggregation *in vitro*, the team, led by Daniel Segal and Ehud Gazit, tested it in transgenic fruit flies expressing human α-synuclein, which model certain aspects of Parkinson's disease in humans, including α-synuclein aggregation and behavioral deficits. Only 38% of the transgenic flies succeeded in a locomotor assay compared with 72% of normal flies. But when transgenic flies were fed mannitol for 27 days, their locomotor assay success rate improved to 70%; furthermore, the amount of aggregated α-synuclein in their brains dropped by ~70% (*J. Biol. Chem.* **288**, 17579–17588; 2013).

The research group next evaluated the effects of mannitol in transgenic mice overexpressing human α-synuclein, a rodent model of Parkinson's disease. Transgenic mice that received intraperitoneal injections of mannitol over a 4-month period had smaller amounts of aggregated α-synuclein in certain areas of the brain and less aggregated α-synuclein overall. No adverse effects of mannitol administration were observed in fruit flies or in mice.

The researchers found that although mannitol administration prevented α-synuclein aggregation *in vitro* and in flies and mice, it did not reverse aggregation *in vitro* or in transgenic mice.

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More studies are needed to further assess the efficacy of mannitol as a treatment for Parkinson's disease, particularly in animal models that more closely recapitulate the development of the disease in humans. But the researchers believe that mannitol may be especially effective when used in conjunction with other medications that have been developed to treat Parkinson's disease but are hindered by the blood–brain barrier. Segal believes that such compounds may be able to "piggyback" on mannitol to cross that barrier, according to a news release from American Friends of Tel Aviv University.

Monica Harrington

DISRUPTING THE DRIVE TO DRINK

For an alcoholic, the taste or even the smell of alcohol can be enough to stimulate the desire to drink. A new study uncovers how such environmental cues trigger the urge to consume alcohol and proposes a means of wiping out drinking-associated memories to help those with alcohol problems stay sober.

Most patients with alcoholism will relapse within the first year of abstinence. Relapse to alcohol abuse is frequently caused by a cue, such as its odor or taste, that was previously associated with the reinforcing effects of alcohol. This association elicits craving for alcohol itself. Disruption of the memory for the cue-alcohol association therefore is expected to prevent relapse.

Memories are thought to become vulnerable when they are retrieved and reconsolidated. The specific signaling molecules and proteins that are required for drug memory reconsolidation remain largely unknown, especially for alcohol. Mammalian target of rapamycin complex 1 (mTORC1) has been reported to contribute to memory processes that are involved in cocaine-conditioned place preference and cue-induced reinstatement. Studies have suggested that disrupting the mTORC1 pathway during the time window of memory retrieval can destabilize the process of memory reconsolidation.

A study led by Dorit Ron (University of California, San Francisco) now shows that alcohol-related cues activate mTORC1 in select regions of the amygdala and cortex in rats and that inhibition of mTORC1 during reconsolidation disrupts alcohol-associated memories (*Nat. Neurosci.* published online 23 June 2013; doi:10.1038/nn.3439). The researchers trained rats to voluntarily consume excessive amounts of alcohol in their home cage by giving them a choice between water and a mixture of water and 20% alcohol for seven weeks. This procedure leads the rats to consume alcohol in quantities that correspond to binge drinking in humans. Then they experienced 10 days of abstinence from alcohol. When researchers gave each rat just enough alcohol for the taste and odor to reawaken alcohol-related memories, mTORC was activated in the central amygdala and in the prelimbic region and orbitofrontal region of the prefrontal cortex.

Immediately afterward, some rats received a drug called rapamycin, which inhibits mTORC1 activity. The rats that received the drug after memory reactivation showed significantly less inclination to consume alcohol over a two-week period. Rapamycin seems to disrupt the reconsolidation of memories that link the smell and taste to the pleasurable effects of consuming alcohol. These findings highlight the mTORC1 pathway as a potential therapeutic target for alcohol abuse.

Kara Rosania