Coming: A drug to sober you up?

Millions will be saluting the coming holidays with more than one glass of their favorite libation. But when the party's over, is there anything available other than coffee to clear the head and stabilize one's equilibrium? Not yet. But an intriguing new drug appears capable of erasing the intoxicating effects of too much alcohol. Not only is it providing insight into the mechanism of intoxication, but it – or a more potent analog – may also prove useful one day in therapeutically sobering up the dangerously drunk or in rehabilitating the alcoholic.

The drug, known as Ro15-4513, was originally synthesized by the Swiss-based Hoffman-La Roche pharmaceutical company for other purposes, explains Peter D. Suzdak, a researcher with the National Institute of Mental Health. But about a year ago Hoffman-La Roche published a preliminary abstract reporting that the drug could block the sedation induced by ethanol. So Suzdak and five colleagues at the National Institutes of Health added it to a battery of drugs they were using to study alcohol's effects on the brain.

"Our data now suggest," he says, "that this drug will block the anti-anxiety or tension-reducing effects of ethanol. It might also block [additional] positive reinforcement effects of alcohol. If the reason an alcoholic drinks is because of these effects, then you might have a drug that's very useful in treating alcoholics."

At least as important, he believes, are the clues the drug is providing about the cause of inebriation. In the brain there are pharmacologically active sites known as GABA-benzodiazepine complexes. On one side of the site is a receptor that binds the neurotransmitter GABA (gamma-aminobutyric acid). On the other side is a receptor for benzodiazepines, anxiety-reducing chemicals like the drug Valium. Between the two, Suzdak explains, is a channel through which chloride ions may pass. The binding of GABA or a benzodiazepine to one of the complex's receptors will open the channel and let chloride into the neuron – an action that "will shut down the firing of that neuron," explains Suzdak.

Though previous studies had shown that animals' behavioral responses to ethanol, benzodiazepines and barbiturates could be similar, the reason had not been established. Research by Suzdak and his co-workers now indicates that the link may be behavioral changes mediated through the GABA system. Previous work by the group had shown that ethanol greatly stimulates the GABA-benzodiazepine complex's uptake of chloride. Their new work, reported in the Dec. 5 SCIENCE, shows that administration of Ro15-4513 blocks ethanol's ability to stimulate the channel's uptake of chloride. Moreover, in doing so, it apparently blocks inebriation in rats – everything from the staggered gait to the release of tension.

This is "a very important link," Suzdak says. For the first time it "suggests that many of the behavioral effects of ethanol are due to changes in the chloride channel."

"Previously, people thought there never was going to be a drug that could [reverse] alcohol's effects," notes neuroscientist George Koob at the Scripps Clinic and Research Foundation in La Jolla, Calif. "I think the significance of their work is showing that there may well be such a safe and useful drug. But I don't think such a drug has been developed yet."

Koob, who has done his own preliminary research using Ro15-4513 in rats, says there are indications this drug is not problem-free. His work suggests it can produce serious "anxiety" in rats. Such anxiety reactions have been described by humans who have been given drugs known to have "inverse agonist" properties against benzodiazepines, he says.

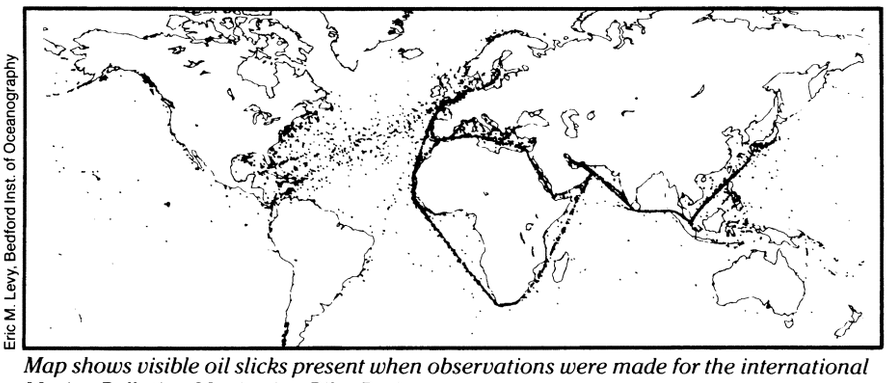
Suzdak challenges that interpretation. Though Ro15-4513 is known to be at least a weak inverse agonist, he says, "if the dose we were using were producing anxiety, we would have been able to pick it up" on the behavioral test they administered to rats. They didn't. Koob suggests this apparent contradiction may be due to differences in the rat strains tested or to the two groups' use of similar but not identical behavioral tests to measure "anxiety" in their animals.

In any case, Suzdak says, "we hope to develop a more potent analog of the drug – one that would have no inverse agonist effects at all." For now, his group is planning tests with nonhuman primates to see whether the current drug is useful in blocking the positive reinforcement effects that encourage alcohol dependence in the chronic heavy drinker.

– J. Raloff

When sea turtles are awash in oil

Each year about 3.5 million metric tons of oil are spilled into the oceans – roughly 1 metric ton for every 1,000 tons extracted, according to 1984 data from the environment directorate of the Paris-based Organization for Economic Cooperation and Development. Most of the resulting surface contamination occurs along ocean tanker lanes and coastal areas. Concerned that sea turtles might be affected by this oil, especially off their nesting beaches in the southern United States, the Interior Department commissioned a consortium of research institutions to conduct the first toxicological study of oil's effects on these aquatic reptiles – all of which are either endangered or threatened species.



Eric M. Levy, Bedford Inst. of Oceanography

Map shows visible oil slicks present when observations were made for the international Marine Pollution Monitoring Pilot Project.

The resulting data show that "the turtles' inability to avoid oil, combined with the fact that they were so strongly affected physiologically by the oil, is probably the worst combination they could have," says Sandy Vargo of the Florida Institute of Oceanography in St. Petersburg, which directed the research project.

In the physiological study, 12 turtles were forced to surface for air for two to four days through seawater covered by an oil slick either 0.5 or 0.05 centimeter thick. Affected animals developed a number of skin problems, including pretumorous changes, lesions and swelling. They also showed immune system changes, such as elevated white blood cell counts.

In a second set of tests, 20 turtles were placed in tanks in which half of the surface area was oiled and the other half was clean. "At best," Vargo says, "the turtles exhibited a weak avoidance of oil – they really didn't seem to distinguish between the two on the basis of tactile, visual or chemical cues."

After the tests, each of the turtles was cleaned, fed, given antibiotics and put in rehabilitative care. Had they not gotten such intensive follow-up care, Vargo says, "they probably would have ultimately died."

– J. Raloff

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