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New Insights

Into the Causes of Alcoholism

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Throughout history, alcoholism has been thought to be the result of poor moral fiber or lack of willpower. Alcohol is a simple, two-carbon molecule, and neither physicians nor scientists could understand why it has such an insidious and devastating effect on the body and personality. Only recently has research begun to reveal alcoholism in its true light: a deficiency disease, often genetic in origin, involving the “neurotransmitters” that act as chemical messengers between brain neurons.

Dozens of scientists in a wide variety of disciplines helped to unravel this complex problem, but in the opinion of the authors, the discoveries made by the following scientists and their colleagues were critical in developing our current view.

V. Davis and M. Walsh in the early 1970's, followed by C. Cohen and M. Collins, found that when alcohol acts on areas in the brain, certain compounds are formed that are precursors to the production of morphine. This work suggested that addiction to alcohol and opiates involves similar biochemical brain mechanisms.

They also found evidence that alcohol is converted to acetaldehyde, and that this substance combines chemically with certain neuro- transmitters in the brain to produce compounds called tetrahydro-isoquinolines (TIQs), some of which resemble morphine. This work further linked alcohol and the opiates

C. Pert and S. Snyder demonstrated that there are specific opiate receptor sites in the brain. In other words, there are areas on certain neurons whose function is to receive opiate molecule, like a key in a lock.

One of the authors (K. Blum) found that certain behavioral effects of alcohol were blocked by such opiate antagonists as naloxone acting at opiate receptor sites. Later work uncovered evidence that the narcotic antagonist naloxone prevents the excitatory effect of TIQs in the central nervous system. This was an early clue to methods of interrupting the effects of alcohol.

R. Myers found that certain TIQs could induce abnormal alcohol intake in rodents bred to have an aversion to alcohol. The phenomenon also could be blocked by the narcotic antagonist naltrexone.

B. Sioquist extended this concept to humans by the discovery of the metabolites of TIQs in urine and cerebral spinal fluid of alcoholics.

A. Goldstein and others discovered the presence of opiate-like substances called endorphins. These substances were soon labeled “opioids.”

C. H. Li found that endorphins are substances containing various amino acids in peptide form. One of these opioid peptides, enkephalin, has been found to consist of five amino acids. It acts as an important

inhibitory neurotransmitter.

L. Stein showed in his brain stimulation experiments with animals that the endorphins are possible mediators of feelings of well-being and euphoria.

B. Lucchi loaded receptor sites with enkephalins that had been “tagged” with radioactivity, and found that TIQs interfere with the binding of enkephalins to those sites. This work suggested that TIQs play a role in the physiology of reward.

Blum now theorized that the difference between alcohol-preferring and alcohol-nonpreferring animals may be due to a deficiency of opioid activity in the central nervous system. Subsequent experiments supported the theory. In one experiment, it was found that alcohol-preferring mice had whole brain enkephalin levels significantly lower than the alcohol-nonpreferring mice. When a variety of animals with different tendencies toward drinking were tested, the correlation between drinking and enkephalin levels was extremely high. Mice with low enkephalin levels prefer alcohol to water. Those with high enkephalin levels prefer water. The enkephalin deficits were found localized in particular brain areas. When the corpus striatum and hypothalamus in other test mice were examined, enkephalin levels were low in alcohol-preferring mice and high in alcohol-nonpreferring mice. From the animal experiments, it was clear that genetic factors were important in opioid levels and alcohol preference; but were other factors at work?

R. McGivern took normal, alcohol nonpreferring rats and subjected them to intense stress by forcing them to swim for 10 minutes in a fish tank filled with icy water. Enkephalin levels in unstressed rats were used as a base. When the brain enkephalin level of half of the stressed rats was tested, it was found to be more than 50 percent lower than in the control rats. When the remainder of the stressed rats were given the free choice of alcohol or water, they now preferred alcohol, a dramatic reversal. Stress, low enkephalin levels, and alcohol preference appeared closely related. To evaluate the effect of heavy social drinking, Blum carried out an experiment in which two groups of hamsters were placed in cages for a period of one year. One group was given water; the other a liquid containing 10 percent alcohol. At the end of the year, the animals that had been exposed to alcohol had markedly reduced enkephalin levels in comparison to animals that drank only water.

A. Hertz showed that following long-term alcohol ingestion by rodents, the synthesis of brain endorphins is suppressed at the RNA level.

A. Gennazinni, working with humans, sampled cerebrospinal fluid from normal social drinkers and from chronic alcoholics. The normal social drinkers had high levels of endorphins; the alcoholics showed significant decreases in endorphin levels.

At first it was thought that direct application of enkephalins might be a solution to the alcohol problem, but the substance degrades so rapidly that very little reaches the brain. There are artificial forms of enkephalins that do not degrade so rapidly, but they are highly addictive.

S. Ehnenpreis theorized that one way to increase enkephalin levels would be to prevent the action of enzymes that normally destroy the enkephalin molecule in the brain.

Exploring this approach, Blum administered a metabolite of l-phenylalanine to alcohol-preferring mice and evaluated their resultant alcohol preference. A control group showed no change. The test group receiving the inhibitor showed significantly increased brain enkephalin levels.

The animals in the test group were then given a free choice of alcohol or water. They showed a significant decrease in alcohol intake.

In a second experiment, two groups of alcohol-preferring mice and a control group of alcohol-

nonpreferring mice were used. One group of alcohol-preferring mice received a saline solution; the other received d-phenylalanine. The three groups, two test groups and a control group, then were subjected to a forced alcohol test. The test group receiving saline consumed four milliliters of the alcohol solution. The test group receiving d-phenylalanine consumed only 2.8 milliliters. The control group consumed 3.0 milliliters of the alcohol solution. The indication was that d-phenylalanine converts alcohol preferring animals into alcohol-nonpreferring animals

Further human studies, and genetic studies of animals during this period, indicated that other substances in addition to enkephalins and endorphins play a role in alcohol drinking behavior, for example: serotonin, dopamine, GABA, and others.

To summarize the results of these experiments: In the normal individual, opioids are being continuously synthesized and are available in the central nervous system in rather high quantities. Both endorphins and enkephalins are released and move across to receptors on adjacent cells. When they reach the cells and activate them, a sequence of events is initiated involving these and other neurotransmitters, that produces a general feeling of well-being.

In the genetic alcoholic, an individual who presumably is born with a deficiency of internal opioids, the picture is different. The synthesis of endorphins and enkephalins is low, and comparatively few of the opioids are released and reach the receptors. As a result, the individual has a feeling of incompleteness, of craving. This situation also may apply to children of alcoholics.

If alcohol is taken in, some is converted first to acetaldehydes and then to TIQs; the TIQs occupy the receptor sites, and a false sense of euphoria is generated. The euphoria quickly passes, and more alcohol must be ingested to regain the good feeling. An additional problem now develops. There are receptors in the cell that measure how much opioid material is available. When TIQs fill the receptors, a signal goes to the synthesizing cells: "No more opioids needed." Consequently, the natural production of opioids is curtailed, and the individual becomes more and more dependent on alcohol.

This work is highly encouraging. We now can understand how the simple alcohol molecule can generate such intense craving, and we are beginning to develop effective, nonhabit-forming methods of correcting neurotransmitter deficiencies, whether genetic or environmental in origin. The most promising method now in view is to use the technique of precursor amino acid loading to prevent the degradation of the brain's natural opioids by such substances as enkephalinase, and to restore the balance of brain chemical messengers.

One nutritional formula that has proved effective in experiments with animals in the laboratory and in use with human subjects is composed entirely of amino acids and vitamins. The goal is to improve brain nutrition, improve the balance of the neurotransmitters, reduce the craving, and help the alcoholic respond more favorably to supportive treatment such as that provided by treatment centers, counselors, and Alcoholics Anonymous.