Science, medicine, and the future

Substance use disorders

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Consumption of alcohol and other intoxicating drugs has serious public health implications relevant to a wide range of people. Recent decades have seen large advances in the understanding of substance intoxication and subsequent problems. The progress was made possible, in part, by developments in the definition and identification of the relevant phenotypes. The American and World Health Organisation diagnostic systems have been made more precise, resulting in more agreement on the definition of dependence.^{1 2} Researchers have also recognised the need to identify and study separately subgroups of dependent people with psychiatric and behavioural syndromes that occurred outside and within the context of their substance use disorder.^{1 3} This article focuses on the recent developments that have improved our understanding of genetic factors that contribute to the risk for alcoholism and our knowledge of the cellular actions of some drugs of abuse and on discoveries that are likely to have direct effects on future clinical management of our patients.

Genetics of alcohol dependence

The process of development and perpetuation of dependence on a substance is highly complex.^{1 4} The

Possible future developments

- Genetic identification of people at highest risk will help identify environmental and psychological factors to be used in prevention
- Identification of different genetic influences will allow treatments to be better matched to patients' specific needs
- Drugs that selectively block the dopamine transporter or D2 dopamine receptors and subsequently blunt amphetamine or cocaine intoxication will help stimulant dependent men and women maintain abstinence
- Identification of endogenous cannabinoids and corresponding receptor subtypes will facilitate the development of safer drugs for glaucoma, muscle spasticity, and severe nausea and help identify antagonists for blocking and reversing cannabinoid effects
- New pharmacological treatments for alcoholism will develop from acamprosate and for cocaine dependence from "immunisation" approaches
- New combinations of treatments will greatly enhance outcomes in rehabilitation

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Fig 1 Factors that may affect development of alcohol dependence

original social, behavioural, and biological factors that contributed to the repeated consumption of high levels of these substances set the stage for the development of further problems. Subsequently, additional social factors (for example, attitudes towards substance consumption and intoxication) combine with additional biological factors (such as acute or protracted withdrawal syndromes) to contribute to the perpetuation of the dependence (fig 1). Recent animal and human studies have focused on potential genetic contributors to various characteristics that might increase or decrease the risk of alcoholism. These include the isoenzyme patterns of the main enzymes that metabolise alcohol (alcohol and aldehyde dehydrogenases), as well as the organism's reaction to the drug.^{3 4}

Recent research in rodents has focused on polygenic determinants of the effects of alcohol that might operate at multiple genetic loci (quantitative trait loci).⁵ These investigations use several methods to identify genetic markers across the genome, including restriction fragment length polymorphisms and simple sequence length polymorphisms (or microsatellites). Studies using recombinant inbred mouse strains (that

is, fully inbred descendants of matings of two inbred strains) have identified several chromosomal regions or "hotspots" that seem to be related to specific characteristics that could affect alcohol consumption. The next step is to search for specific genes already known to reside in that chromosomal region which might contribute to alcoholism.

Several chromosomal regions in mice have been identified as potentially important. Quantitative trait loci on mouse chromosomes 1, 4, and 11 seem to influence the severity of alcohol withdrawal,⁵⁻⁷ and regions on chromosomes 1, 2, 8, 11, and 15 appear to affect the intensity of reaction to ethanol as measured by response to anaesthetic.⁸ Hotspots on chromosome 9 have been related to alcohol hypothermia and ataxia (and tolerance to these effects)⁹ as well as to a preference for alcohol over water.^{5,7} The implicated regions of chromosome 9 also contain the dopamine D2 receptor and the serotonin 1B receptor, which might serve as candidate genes for future work.⁵

The chromosomal regions identified, however, are mostly quite large, and several steps have been used to test for the potential relevance of specific genes. One approach is to use a knockout animal strain in which the active gene is deleted. For example, a mouse strain has been developed which is deficient in the serotonin 1B receptor.¹⁰ These animals consume twice the volume of alcohol as wild type mouse controls, voluntarily drinking ethanol solutions as high as 20%, and are also less sensitive to ethanol induced ataxia, while developing tolerance to these effects more slowly.¹¹

Human studies

Studies in humans have the advantage of being in the most relevant species, but it is more difficult to control the environment and impossible to manipulate genetic material. The most systematic recent investigation is the collaborative study on the genetics of alcoholism, a genetic pedigree study.^{3,12,13} This project is collecting data on over 9000 people and is searching for multiple traits likely to be associated with risk of alcoholism in the almost 3000 men and women expected to have potentially informative pedigrees for whom genetic material is also being obtained.

In addition to supplying valuable data on the natural course of alcohol and drug dependence,¹⁴ this study has begun to generate information on possible genetic linkage to specific traits. Analyses are focusing on personality characteristics, the intensity of reaction to alcohol, and more specific physiological phenomena. Among the latter is the P3 wave, the positive polarity wave observed roughly 300 milliseconds after a rare but expected stimulus in a brain event related potential electrophysiological paradigm.¹² A subgroup of alcoholics have low amplitude P3 waves that exist as a trait observable before the onset of alcoholism and which continue despite long term abstinence. P3 amplitude seems to be linked to chromosomes 2 and 6.¹²

The collaborative study population is also being used to search for genetic determinants of a low level response to alcohol in humans. The work is based on animal studies that showed less intense motor performance impairment or shorter alcohol related sleep times in most rodent strains that consume higher amounts of alcohol and on a 15 year prospective study

Fig 2 Role of dopamine reuptake transporter in cocaine addiction. Cocaine blocks reuptake of dopamine, prolonging activation of the dopamine receptors in the synapse. Adapted from Leshner¹⁷

of 453 sons of alcoholics and controls.¹⁵ In sons of alcoholics, smaller change in hormones, less intense subjective feelings of intoxication, or less reduction in motor performance related to alcohol at age 20 predicted severe alcohol problems 10 to 15 years later. This explained a large proportion of the ability of family history to predict subsequent alcoholism.

Studies of the factors that increase or decrease risk of alcoholism, and identification of the contributing genes, should help in developing more focused approaches to prevention and treatment. Regarding prevention, the study of individuals at highest risk of future alcohol or drug dependence who subsequently do and do not develop full blown dependence might reveal protective environmental and psychological factors amenable to change. Genetic studies may also identify subgroups of substance dependent people who have special treatment needs. For example, people whose raised risk of dependence is due to personality or cognitive factors might respond to different regimens than those whose problems are rooted in their physiological response to the addictive substance.

Receptors and drugs of abuse

Important advances were made in the 1980s and 1990s regarding the mechanisms of action of opiates on the brain.¹⁶⁻¹⁸ Similar progress has been made with other drugs.^{17,19} For stimulants such as cocaine and amphetamines recent work has emphasised the importance of the dopamine reuptake transporter and dopamine receptors in the effects of these drugs on the brain. The dopamine reuptake transporter helps control the concentrations of dopamine in a synapse by rapidly carrying the transmitter back into the pre-synaptic cells. Cocaine strongly binds to the transporter, thus blocking reuptake and causing more persistent dopamine effects in the synapse (fig 2).^{17,20} The importance of this phenomenon was tested in knockout mice without the gene for the transporter. These animals showed no significant behavioural or biochemical changes when given cocaine or amphetamine. The results raise the possibility of developing drugs that affect the action of the transporter to treat stimulant dependence.²¹ The goal would be to dampen a person's response to amphetamines and cocaine to a degree where taking them is no longer rewarding.

Also of interest is the different effect of dopamine on different dopamine receptors (including D1, D2, and D3 variants).¹⁹⁻²² Rats given D2 agonists rapidly restarted self administration of cocaine, yet D1 boosting drugs had little or no effect and actually suppressed cocaine seeking behaviour.²³ Thus, drugs that selectively block D2 receptors might decrease the risk of relapse in stimulant dependent people with fewer side effects than current treatment.

A third important discovery is related to endogenous cannabinoids that might have specific actions on cannabinoid receptors in the brain.²⁴⁻²⁵ These substances might be important in the effects of cannabis and some other drugs, and could even mediate the craving for chocolate.²⁶ The substances of interest are the arachidonic acids and *N*-acylethanolamine compounds anandamide and *N*-palmitoethanolamine, which activate cannabinoid B1 and cannabinoid B2 receptors respectively. These chemicals seem to behave as neurotransmitters; they are synthesised by neurones, levels in the synaptic space are controlled by reuptake as well as by specific enzymatic actions, and they affect receptors. Such findings may help researchers and clinicians understand more about the mechanisms of action and the consequences associated with the cannabis-like drugs. The result could be more effective and safer drugs for the treatment of glaucoma, muscle spasticity, and severe nausea or anorexia, and the production of cannabinoid antagonists that might facilitate abstinence from cannabis drugs by blocking the high.

New treatments

The treatment of any substance use disorder involves a combination of steps aimed at the alleviation of withdrawal symptoms (if needed) along with a combination of behavioural, cognitive, and pharmacological approaches integrated into rehabilitation.²⁷⁻²⁸ The goals are to maximise commitment to abstinence, help rebuild a life free of substances, and to develop strategies for preventing relapse.

Unsurprisingly, there are few specific and standardised rules for the current generic treatment approaches. Thus, we need to understand more about the best way to match treatment to a patient during rehabilitation.²⁹ A study evaluating the best match has recently been published, and the results also showed the marked improvement in functioning likely to be observed with almost any carefully applied therapeutic regimen.³⁰

However, no panacea for the treatment of these complex substance use disorders has yet appeared, making the search for additional therapies that might add even modestly to the treatment outcome important. Several studies have evaluated two drugs for the treatment of alcohol dependence. The first is calcium acetylhomotaurinate, or acamprosate. This drug has a chemical structure similar to the amino acids taurine and γ -aminobutyric acid, stimulating the inhibitory actions of γ -aminobutyric acid on neuronal transmission while antagonising the excitatory effects of glutamate.³¹⁻³² A study in Austria gave almost 500 alcoholics either 1.3-1.9 mg per day of acamprosate or placebo over 12 months. A higher proportion of those taking acamprosate remained totally abstinent (18.3%

v 7.1%, respectively) and the group was abstinent for more days (139 *v* 104), with no significant difference in the pattern of side effects.³¹ A German study that evaluated 272 patients for 48 weeks found that 43% of those taking acamprosate versus 21% on placebo remained continuously abstinent, with 224 versus 163 days of not drinking in the two groups and a lower dropout rate for those taking the drug (41% *v* 60%).³² Acamprosate represents a new class of pharmacological drugs for alcohol dependence and might pave the way for even more effective interventions in the future.

The other pharmacological approach involves prescribing opiate antagonists.³³⁻³⁴ The early results in patients who received naltrexone for 12 weeks have been corroborated in investigations using nalmefene, a pure opiate antagonist with a longer half life and less effect on the liver. In a 12 week study of 30 patients given 10-80 mg nalmefene per day there were few differences in the proportion who returned to alcohol, but those receiving the highest dose were more likely to remain in stable remission (62% for 80 mg/day *v* 0% to 37% for 10 or 20 mg/day).³⁵ Preliminary data from an expanded sample of 105 subjects treated for 12 weeks with either 20 or 80 mg of nalmefene or placebo also gave promising results. Future research with opiate antagonists is likely to enhance our understanding of the effects of alcohol on the opiate and associated dopamine reward brain systems and consequently our knowledge about alcohol related psychological and physical problems. Such research might also lead to the identification of additional treatments for alcohol dependence, with the possibility that the combination of acamprosate-like drugs with opiate antagonists might prove even more effective than either class of drugs alone.

Finally, a potential advance has been reported for the treatment of cocaine dependence.³⁶ Rats given cocaine which had been conjugated to a foreign carrier protein to stimulate an immune response produced antibodies that recognised and bound to future doses of cocaine. When immunised animals were given 15 mg/kg of cocaine they had lower brain levels of cocaine and less behavioural stimulation, including 42% lower

An energy potential contour map for dopamine. Research is focusing on dopamine and its receptors

levels of ambulation, than non-immunised rats. The overall goal is to develop a treatment for cocaine dependence that blocks the intoxication or reinforcing effects of the drug while having little effect on neurotransmitter functioning. If replicated and shown to be safe, this innovative approach is likely to lead to a series of treatments for different drugs of abuse.

Conclusion

Recent discoveries relating to genetics, the cellular mechanisms of some drugs, and specific treatment approaches each point towards possible new interventions that might greatly affect treatment of substance dependence. As is true of most advances, however, a great deal of work will need to be done to determine the optimal clinical applications of these discoveries. In addition, clinicians and researchers will have to carefully safeguard the rights and safety of patients while incorporating these new genetic and biological components into our prevention and treatment efforts.

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One hundred years ago Cycles and motors

The twenty-first annual exhibition of cycles and cycle accessories is now being held at the Royal Agricultural Hall, Islington. In spite of the great increase in the use of cycles during the last few years, it cannot be said that any advance in principle, either of material or construction, has been made. Of alloys—mostly of aluminium—a number are now on trial, but none appear to compare with steel in point of intrinsic strength; and of methods of propulsion to replace the chain there is an abundant supply, but the chain works with an economy very nearly approaching the theoretical, and most of the proposed substitutes involve joints or gearing in which the loss from friction is far greater. We had hoped to find some advance in motor cars sufficient to render them fit for rough use in country practice. But as at present made they will, we fear, be apt to prove either too

expensive or too complicated for the rough work of general practitioners in country districts. But although we have no intrinsic advance to record, a visit to the show is well worth making. Few people have any idea of the amount of really fine work a modern bicycle requires. Built as it is with the smallest possible margin of safety, it gives an even smaller margin for poor work. As an example of the skill and power required to turn out even such a small part of a machine as the hub, the American Hub machine is perhaps typical. This machine turns and drills from the solid bar, hubs at the rate of fifteen an hour, each one perfect in every detail. To those whose interest in cycling matters is not simply a matter of record breaking, the machinery shown at the Stanley show will be the most interesting feature. (*BMJ* 1897;ii:1603.)