abstract analytical logic to careful experiment with single neurons or fractions of single neurons.

Some particular techniques that should be noted

No one can profess to be competent enough to comment on all the various techniques that can be used to study concept formation. A few of the methods that can be used and which are not commonly used in India are:

1. *Histological techniques*. (i) intracellular marking of neurons by injecting the marker into the neuron using microelectrodes and (ii) image analysis techniques using computers.

2. Modelling and neural network analysis.

3. *Kinematic analysis of movements*. The subject is instructed to react in a given manner. He is then presented with a given environment. The subject's movement is recorded and analysed. From the results, one can develop ideas regarding the manner in which concepts are formed. One must make special mention of the work by Jeannerod. Again the study done at Queen's Square on a deafferented man requires a special mention.

4. *Teaching methods*. In other countries, there is a determined effort to develop techniques of teaching. Such teaching methods are developed and evaluated for exceptionally gifted children, mentally and physically handicapped children and normal children. In all cases there is an attempt made to understand the way concepts are formed and understood by the pupil.

5. Studying the development of the mind and brain in the new-born and very young children. This is done in other countries by studying topographic brain mapping or with appropriate psychological studies.

The Indian scene

Basically, the problem in India is that very few laboratories do sustained work on various aspects of the nervous system/mind, delving deeply into the relationship between the two. Secondly, we do not strive to publish our work in the best journals. Unfortunately, unless the Indian researcher publishes in first-class indexed journals, the work will go largely unrecognized. This is because the rejection rate of such journals is very high and, hence, one has to compete with researchers from all over the world to publish in these journals. This ensures that only excellent work will be accepted by these journals.

Perhaps no Indian laboratory has particularly studied concept formation. However, some laboratories have concentrated on aspects that are highly related to the subject. Various excellent studies on tracing pathways, both sensory and motor, have been done. This is an important step towards understanding the physical basis of the mind. Of special mention are the Department of Anatomy at the All India Institute of Medical Sciences, The Department of Animal Behaviour and Physiology at the Madurai Kamaraj University, The Department of Zoology of the Sri Venkateswara University, Post-Graduate Centre, Kavali, The Tata Institute of Fundamental Research, The Centre For Artificial Intelligence and The Neurophysiology Laboratory of The Department of Neurological Sciences, Christian Medical College and Hospital, Vellore. At all these places, some sustained work on some particular aspect of concept formation has been in progress. Unfortunately, none of these laboratories may claim to have had 'concept formation' as the primary subject of study. However, they have all contributed in some way to the understanding of the physical basis of the mind.

Neurobiology and drug abuse

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THE phenomenal growth in neuroscience research over the last decade has led to a better understanding of the biological basis of drug abuse and dependence. Contributions from various disciplines like neuroanatomy, neurophysiology, neurochemistry, molecular biology and behavioural pharmacology, along with technological advances, have helped us to achieve a holistic view. Interactions between biological, pharmacological and behavioural factors, rather than isolated defects in any one of the areas, are crucial to the understanding of the complex nature of the topic.

There are various chemical compounds, both natural and synthetic, which are addictive. This review will concentrate mainly on opiates, alcohol and benzodiazepines. The literature on nicotine and cannabis is very extensive and deserves attention separately and,

hence, is not covered here. This review is divided into four sections. The first section deals with the neurobiological basis of sensation seeking, tolerance and dependence. The next section discusses the correlation of neural activity with behaviour. CNS (central nervous system) deficits due to chronic use are dealt with next. Finally, we discuss the biological vulnerability to drug abuse. Highlights of studies published by Indian researchers and future research issues are also discussed.

Effects of drugs on CNS and anatomical sites of action: A review

Many drugs of abuse have the capacity of altering psychomotor and sensory functions through effects on CNS. The impairment is seen following both acute and chronic drug administration.

Among the various effects, sensation seeking and euphoria are central in understanding biological disposition towards drug abuse. It has been seen that electrical stimulation of certain areas in the brain is rewarding. Thus, the animal having been exposed to artificial stimulation of such an area would voluntarily indulge in self-stimulation to seek pleasure. In animal experiments, these effects are sufficiently reinforcing to make the animals work towards self-administering drugs[1]. This phenomenon of intracranial self-stimulation causes euphoria, reflected by lowering of the threshold (intensity of stimulation) for reward and is seen with drugs like morphine, cocaine and amphetamine[2].

There have been many experiments to determine the sites of action of these drugs. Mesocorticolimbic dopaminergic pathway has been implicated. The connections between the ventral midbrain and the ventral forebrain is the starting point of the neurobiological reward circuit. Anatomically, the neural circuit connecting medial forebrain bundle, olfactory tubercle, septum and nucleus accumbens with ventral tegmental area and hypothalamus is the major conducting system[3]. Esposito *et al.*[4] reported that stimulation of implanted electrodes in VTA, dorsomedial thalamus and median forebrain bundle lowered the reward threshold without influencing the rate of response.

Receptor pathways

Another way of investigation has been to study the effects of drugs on various receptors. Opiates exert their effects through opiate receptors in the brain and dependence is produced mainly through μ-receptors. Additionally, dopamine receptors are also involved. As a matter of fact, it has been suggested that opiate reward system is mediated through both dopaminergic and μ-receptor pathways[5]. Ethanol self-administration in rats has been reduced by dopamine receptor antagonists[6]. In general, reinforcing effects of various drugs of abuse are mediated through dopamine (D1 and D2) receptors[3]. It has been possible to establish this through *in vitro* autoradiography[7].

Opiates

There are a variety of opiate receptors differing in ligand specificity and anatomical locations. Generally, narcotic agonists and antagonists react with more than one receptor subtypes. Only a few opioid peptides have absolute specificity for any one subtype[8]. Further, the dynamic nature of the receptors also influences the effects. The affinity may change following chronic drug use, viz. upregulation of the receptors in the presence of antagonists[9].

Following prolonged use, tolerance and dependence develop. Due to chronic exposure, the CNS develops adaptive changes to depressant effects of morphine and related compounds, resulting in tolerance. Dependence, as manifested by withdrawal symptoms, is an imbalance of this homeostatic state. These, in turn, are associated with both enzymatic and tissue level changes at the receptor level.

In some brain regions the effects of opiates include inhibition of adenylate cyclase. Long-term use leads to compensatory increase in adenylate cyclase activity and excessive production of c-AMP is partially responsible for excitability of neurons during withdrawal[10]. Regulation of adenylate cyclase activity would, hence, be important in development of dependence. Physical dependence on morphine can be blocked by influencing G-protein, an inhibitor of adenylate cyclase activity[11].

Long-term administration of opioids decreases the synthesis of pro-enkephalin in the striatum and a lag in production of pro-enkephalin might also explain opiate withdrawal phenomenon[12].

Action of ethanol

Most of its action is mediated through its ability to alter physicochemical properties of the cell membrane which has a lipid bilayer structure. Cholesterol and phospholipids play an important role in maintaining the fluid property of the membrane. Acute alcohol exposure leads to increased membrane fluidity. Chronic use leads to adaptive changes and rigidity of the membrane. This decreased fluidity is brought about by alteration of the membrane cholesterol–phospholipid ratio[13, 14]. These changes in turn influence Na^+- and Ca^{2+}-channel-dependent release of neurotransmitters and ATPase activity[15].

Acute administration of ethanol enhances adenylate cyclase activity in the brain and chronic use reduces the

activity. In humans, decreased activity of adenyl cyclase in platelets and lymphocytes is considered a trait marker of alcoholism[16]. It would thus appear that acute administration of alcohol causes change/disorder and chronic use reduces the above effect, indicative of a tolerant state. However, the link between membrane lipid changes and functional alterations during chronic use is still unclear.

Ethanol also exerts its influence through various neurotransmitter changes. Elevated level of dopamine in the nucleus accumbens encourages animals to drink alcohol as also seen with low 5-hydroxytryptamine (5-HT)[17]. Depletion of brain serotonin has been shown to delay the development of tolerance to certain effects of alcohol[18].

Yet another mechanism is the influence of acetaldehyde on biogenic amines. Acetaldehyde, a product of alcohol metabolism, condenses directly with dopamine and norepinephrine. Products like tetrahydro-isoquinoline (TIQ) and tetrahydropaveraline (THP) act as false neurotransmitters and promote alcohol consumption in rats when injected intraventricularly[19, 20]

The intoxicating effects of ethanol are also implicated through its action on GABA. Ethanol potentiates GABA-mediated CNS inhibition. Anxiolytic effects of GABA are mediated through Type-I receptors (GABA-A) and may be the major factor responsible for reinforcing properties of ethanol[3]. Finally, GABA-inverse agonists reverse some of the behavioural effects of alcohol[21].

Some of the above findings have also been confirmed through human cerebrospinal fluid (CSF) studies. Low CSF levels of 5-HIAA and HVA have been found among subjects showing florid alcohol withdrawal[22, 23] Alternatively, Ballanger *et al.*[24] suggested that alcoholics have low levels of pre-existing brain serotonin. Clinical studies have also shown that 5-HT blockers like fluoxitine can significantly alter alcohol consumption[25, 26]. Roy *et al.*[27] in their review suggested that a subgroup of alcoholics have a defect in their central serotonin level. Among them alcohol abuse starts at an early age.

Benzodiazepines

Benzodiazepines enhance GABA-ergic transmission. Their dependence liability is possibly due to their anxiolytic property, mediated through Type-I receptors located in the cerebral cortex and cerebellum, benzodiazepine withdrawal, reduced synthesis of 5-HT and increased levels of 5-HIAA[28].

Manifestation of tolerance and dependence in man

In human experiments, dependence is inferred by the presence of a large number of signs and symptoms due to abstinence. Tolerance is evident by the reduced response to a given dose of the drug(s). However, all the signs of tolerance and dependence are not parallel; moreover, tolerance and dependence are difficult to quantify on occasions. Often, at the functional level, the acute effects of a drug differ across species. Furthermore, some physiological functions manifest complete tolerance, some only partial and some show no effects. For example, following chronic administration of morphine, analgesia, euphoria and EEG, changes become completely tolerant, pupillary changes partially tolerant and gastrointestinal motility does not become tolerant[29]. These are further complicated by simultaneous stimulation of CNS activities which are antagonistic, e.g., sympathetic and parasympathetic nervous system. Tolerance to certain drugs like benzodiazepine in humans is both functional and metabolic. These are further influenced by long duration of action of the parent compound and the presence of active metabolites. It has thus been felt that the role of other factors, besides neurotransmitter and receptor changes, should also be studied[30]. Organismic factors like motivation, self-administration and conditioning are important in understanding dependence.

Correlating dependent behaviour with neural activity

The word dependence is used in at least two different ways: (a) physical dependence and (b) a more general term, abuse liability of a drug. Physical dependence connotes the consequences of chronic exposure to a drug, i.e., tolerance and withdrawal symptoms. The term 'abuse liability' refers to a complex behavioural phenomenon leading to repeated use and possible dependence. Assessment of functional consequences of drug intake would include a study of psychopharmacological and behavioural aspects leading to repeated use. Investigation of behaviour, along with the anatomical site of action and the mechanism of action, provides an insight to an understanding of the process of drug dependence[31].

Pharmacologically, it is known that only certain compounds like opiates, cocaine, amphetamine, barbiturates, ethanol and nicotine are self-administered and have positive reinforcing effects[32]. The reinforcing property of a compound is understood as its ability to cause euphoria and functional enhancement like anxiety reduction. Other antecedent events like drug discrimination and consequent factors like euphoria contribute to the development of dependence. The relative contribution of these two processes can vary[33].

Physical dependence potential is assessed by its pharmacological and physiological action over a wide range of doses. Separate sets of experiments are required to study stimulus properties, including behavioural performance.

Animal testing procedures include quantifying acute and chronic effects of a drug. These include assessment of spontaneous motor activity, forced motor activity, electroencephalogram and behavioural performance like seeking food and water consumption, aggression and avoidance of painful stimuli. Drug self-administration is measured by automated drug delivery through intravenous catheter. Methods for assessing dependence potential in rats were first developed by Akera and Brody[34]. Procedures for assessing the discriminative stimulus of drugs have now been developed for primates also. In experiments for studying self-administration, typically, the animal presses a starting lever, after which it must press the appropriate lever on the other side of the cage in order to prevent shock delivery. The appropriate lever is determined by whether the animal had received a saline injection or an injection of the training drug (usually a dependence-producing substance). In such a situation escape behaviour is established by presentation of a positive reinforcer, i.e., the drug. The stimulus properties are tested over variable doses[35]. In another paradigm, the animals are trained to receive food following lever presses to deliver an injection of an opioid[36]. The drug acts as a secondary reinforcer and, subsequently, becomes the conditioned reinforcer. In both the situations the drug acts as a reinforcer. Physical dependence and abuse as discussed earlier frequently occur together, though relative contribution of either of the factors can vary with different pharmacological substances. In spite of these advances, validity of neurochemical, physiological and behavioural methods to assess dependence continues to be debated. To be addictive, a drug should have positive reinforcing property and be differentiated from other such substances.

Abuse liability of drugs in humans

Assessment of abuse potential of psychoactive drugs in clinical studies is used in regulatory decision-making process for a pharmacological compound for marketing by pharmaceutical industry, the basic assumption being that there are drugs of abuse that will not be pursued for marketing by the pharmaceutical industry. In a number of situations, preclinical data will suffice to determine the dependence potential and abuse liability of a drug. However, it must be realized that interpretation of preclinical data must consider biological differences between animal species and humans. Situations have arisen wherein drugs are passed through animal screens only to show abuse liability in humans. Metabolism, elimination, half-life of a drug and effects could be very different in man. Determination of subjective effects, changes in mood states, drug liking and discriminative stimulus properties are used to compare a test drug against a standard (known substance). The primary emphasis is on dose–response characteristics and reliability in the production of effects[37]. By and large it has been reported that substances which have high intrinsic pharmacological property, high oral bioavailability, low protein binding, small volume of distribution and high clearance have greater reinforcing properties. These substances enter rapidly into specific brain sites. On the other hand, substances which have high intrinsic pharmacological activity, small volume of distribution, long half-life and low clearance promote physical dependence. High lipid solubility is also associated with rapid entry into the brain. All these data are used to categorize a substance as a low- or high-dependence-producing substance[38]. The pioneering studies of drug abuse liability among humans were carried out on volunteers by Martin and Fraser[39]. These volunteers served as subjects in studies of biological and behavioural effects of abused substances. The studies also led to the development of various research instruments for clinical studies. The underlying principles to predict abuse liability of substances are: (a) the subjective effects including the CNS changes which can be quantified and (b) that subjective response can predict the reinforcing action of a drug. Several research strategies have been evolved for such studies. These include the assessment of (a) tolerance, (b) physical dependence (withdrawal symptoms), (c) discriminative property and (d) reinforcing efficacy[40]. Measurement of euphoria or pleasure following drug administration has been crucial in all these studies. It has been further noticed that development of physical dependence is neither necessary nor sufficient to maintain drug-seeking behaviour. The advances described contributed to the development of a standardized questionnaire to compare the addictive properties of a wide range of drugs. Some of the available instruments are:

(a) Single Dose Questionnaire (SDQ)[41].
(b) Addiction Research Center Inventory (ARCI)[42].
(c) Profile of Mood States (POMS)[43].

These instruments predict that if a new drug causes euphoria, sedation or intoxication as measured by ARCI, or elevation of SDQ or POMS scores, then it is like morphine and has strong addiction liability.

The above self-reported measures have been validated by increase in alpha activity in EEG recordings[44] and increase in plasma ACTH levels[45]. Similar effects have also been observed following ethanol administration[46]. Subjective self-reports of euphoria occurred between 10 and 15 minutes after consuming alcohol, accompanied by an increased alpha activity in the EEG. Even topographical distribution of EEG alpha activity has been demonstrated. Low-amplitude slow-frequency alpha activity has been recorded on the entire scalp, wherein high-frequency alpha has not been found in the frontal cortex[46]. It is thus apparent that neuroendocrinal and neurophysiological correlates have

been documented following alcohol/drug/placebo administration.

Drug discrimination also requires investigation. Test drugs (new substances) are compared to reference drugs (known drugs) as regards their effects. Drugs having similar effects are presumed to have similar abuse liability. In experimental situation, subjects without prior drug experience are asked to assess the similarity to the reference substance after exposure in controlled experimental situation. The behavioural procedure involves operant conditioning. The subjects are trained to emit different responses in the presence of different drug conditions[47]. Certain responses are reinforced on occasions by monetary payment also. These experiments help in categorizing stimulus properties of drugs with overlapping profiles of action. By and large, correct discrimination is appropriately dose-related. Although it is not a direct index of abuse liability, it predicts the abuse potential of a new substance.

Among humans the craving for a drug intensifies in the presence of cues related to drug availability. Operant response to obtain drugs is emitted in the presence of withdrawal symptoms.

Summarizing, the relationships between drug self-administration, drug discrimination and self-reported effects are manifold. By and large, studies conducted in animals and humans within behavioural contexts are comparable in predicting abuse liability.

CNS deficits due to prolonged use of drugs

Imaging of the brain

Quantitative imaging of neuroreceptors has recently become feasible through positron emission tomography (PET). However, dynamic indices of receptor activity like measures of uptake and turnover still do not tell us adequately about the functioning. *In vivo* validation of the relationship between neurotransmitter uptake, turnover measures or receptor concentrations is still lacking. Measuring or even estimating the actual delivered dose of a labelled ligand to the brain is complex. Validation among humans is a formidable task and the technology is prohibitively expensive[48]. Notwithstanding these difficulties, it is now possible to image in real-life situations the distribution and localization of specific receptors and biochemical parameters, as illustrated in opiate receptors using 11C carfentanil, where highest radioactivity was seen in amygdala, thalamus and basal ganglia[49]. Most human studies on alcohol intoxication suggest that higher doses of alcohol produce cerebral vaso-constriction and reduced cerebral blood flow among chronic alcoholics[50]. PET scan studies showed reduced post-ethanol glucose metabolism for the entire brain[51, 52].

Similarly, structural changes due to chronic drug abuse have been documented. Charness and Dela Paz[53] using MRI demonstrated ventricular enlargement and damage to mammillary bodies among alcoholics with Wernicke's encephalopathy. The latter is associated with memory loss and amnestic disorders. Earlier, CT scan studies showed that 38–78% of the patients with alcoholism showed widening of cortical sulci and ventricular dilatation. Age was one of the confounding variables determining the assessment of CT scan changes[54, 55]. Only a few reports are available among heroin abusers, and causes leukoencephalopathy[56].

Electrophysiology

Advances in electrophysiology have permitted studies of functional deficits in the brain among alcoholics. Earlier, the resting-state EEG showed excess of high-frequency waves and deficiency of alpha activity[57]. Pollock *et al.*[58] showed that the EEG of alcoholics reflected greater sensitivity to alcohol challenge than controls.

Event-related potentials (ERP) reflected further subtle dynamic changes among alcoholics. During long-term abstinence, decreased ERP amplitudes and reduced late component (N1) persisted[59]. In dependent state, a marked decrease of auditory brainstem potential (BSP) amplitude has been seen. P300 amplitudes are significantly reduced or absent to target stimuli. In withdrawal, shortened BSP latency has been observed. These suggest limbic system deficits. Hyperexcitability as manifested by prolongation of brainstem latencies may reflect the fluidizing effect on neuronal membranes[59, 60]. Differences in electrophysiological response to alcohol challenge dose have also been reported. Findings from Japan suggest that flushers are more susceptible to delayed BSPs on alcohol intake than nonflushers[61]. Only one study on narcotic addicts showed reduced P300 amplitude[59].

Foetal alcohol syndrome (FAS)

In 1973, certain birth defects were observed among children of alcoholic mothers[62]. Since then, a great deal of clinical and basic research has taken place on FAS. Using animal models, a variety of sensorimotor defects have been reported. These include visual, auditory and motor incoordination, optic nerve hypoplasia[63], hearing loss[64] and gait asymmetry[65]. These rat offsprings were poor feeders[66]. Normal growth, development and learning were also affected following prenatal exposure to alcohol.

Clinical studies have shown that FAS comprises of growth retardation, craniofacial anomalies, CNS dysfunction and major organ malformation[67]. Some

improvement did take place during follow-up[68]. As yet, the relationship between the critical period of exposure and the dose of alcohol has not been established. Some studies have, however, reported that peak blood alcohol level is more important than the total alcohol consumed during this period. Several factors like foetal hypoxia, alteration in prostaglandins and acetaldehyde levels have been proposed to explain the underlying mechanism[69].

Biological vulnerability to drug abuse

Genetic factors

Research carried out over several decades has implicated genetic factors in the etiology of alcoholism. Though alcoholism tends to run in the same families, genes are not the sole determinants of alcoholism. Genetic factors may also produce idiosyncratic biological response to drugs. These factors can operate by eliminating protective factors.

Ethnic differences in the metabolism of alcohol have been known for years, e.g., a higher rate of alcohol metabolism in Chinese, Japanese and Native Americans. In general, Japanese and other Orientals have a relatively lower rate of alcohol-related problems[70]. Diverse studies among American subjects have shown that on an average about 40% of alcoholics had an alcoholic parent. Male relatives had higher rate of alcoholism than females[71]. Although family, twin and adoption studies all support the importance of genetic factors in alcoholism, very few studies have identified the specific basic genetic defect. None of the studies suggest a simple Mendelian, dominant, recessive or sex-linked transmission. Even more, lack of concordance for alcoholism in first- and second-degree relatives also excludes a simple polygenic mode of inheritance[72]. In other words, environmental factors contribute significantly along with genetic factors in the development of alcoholism.

A number of biological markers or mediators interacting with environmental factors have been investigated. Certain studies have tried to categorize subjects as high/low-risk. It has been reported that high-risk individuals (family history positive – FHP) develop greater static ataxia, poorer perceptual–motor functions[73], and higher levels of acetaldehyde following consumption of alcohol as against controls[74]. Tabakoff *et al.*[75] reported low platelet MAO activity associated with alcohol abuse, which was perceived to be a genetic vulnerability for alcoholism.

Pollock *et al.*[58] noted a deficient alpha rhythm in EEG among FHPs. Quantifiable analysis of EEG revealed that the children of alcoholics were different from the children of non-alcoholic parents with respect to alpha frequency. ERP studies showed that 36% of sons of alcoholics had low-amplitude P300 even without use of alcohol.

The above review discusses mainly the trait markers as regards etiology of alcoholism. There are a host of markers, identified as state markers, i.e., defects observed after development of alcoholism. These are not discussed here as they would not constitute biological vulnerability to alcoholism.

In contrast to alcoholism, little is known about genetic factors that contribute to other drug-dependent abuse (viz. heroin or cocaine). In terms of aetiology, maximum attention has been paid to psychosocial factors that promote drug abuse[76]. There are reports, however, which suggest that pattern of inheritance for drug abuse may be similar to alcoholism. Drug abusers frequently abuse alcohol though not *vice versa*[77]. Despite advances, knowledge on genetic vulnerability is still rudimentary. It does not allow us to use the available information about individual differences to decide differential treatment or prognosis[78].

To conclude, it can be seen that there have been significant advances in neuroscience methods in drug abuse research. New approaches and techniques have been developed over the last ten years. Investigative techniques in neuroanatomy, neurophysiology and molecular biology, along with behavioural pharmacological research, have been developed. These advances have been largely possible due to multidisciplinary approach. A substantial gap still exists between receptors, mechanism of action, issues like drug taking, self-control and development of drug dependence. Szara[79] suggested that the following questions should be addressed:

(a) Are the methodologies sufficiently sensitive?
(b) What kind of specific hypothesis ought to be formulated to make best use of current technology?
(c) What level is the study aimed at (molecular, synaptic, transmitters, animal, human)?
(d) What kind of subject population, including humans, are required for further experimentation?
(e) What should be the most appropriate design?

National literature

Overwhelmingly, the research on drug abuse in India has been on clinical and social issues. Few researchers have looked into neurobiology of drug dependence. Some data, though scanty, are available.

Pre-clinical studies

Sharma *et al.*[80] reported that development of tolerance to opiates could partially be due to decoupling of opiate

receptors from adenylate cyclase. Further, they suggested that ascorbic acid suppresses the increase in the levels of c-AMP in NG 108-15 hybrid cells[81]. Thus, ascorbic acid may prevent development of tolerance to narcotics.

Kulkarni and Sharma[82] reported that chronic benzodiazepine administration causes flux of Ca^{2+} ions into GABA receptor complex. This would suggest functional changes due to benzodiazepine dependence.

Shetty[83] reported that catalase activity in rat brain could be induced after chronic ethanol ingestion. This would suggest that more ethanol is oxidized in brain, which in turn leads to development of tolerance and increased formation of acetaldehyde in the brain.

Clinical studies

Increase of cholesterol and decrease of phospholipid in erythrocytes of alcoholics have been reported[84]. The findings were similar to those of preclinical studies. It was also reported that alcoholics had decreased erythrocyte ALDH activity. This could suggest a trait marker of alcoholism[85].

Absence as well as reduced amplitude of contingent negative variation (CNV) were reported among abstinent alcoholics[86]. About 50% of the abstinent alcoholic patients did not show the P300 component. The mean amplitude in alcoholics was less compared to the control group. Reduced latency of Bereitschaft's potential (BP) was also reported among abstinent alcoholics. These studies suggest functional CNS deficit in the form of disintegration of volition, arousal and attentional processes[87].

Majority of the studies are on alcoholics. Biological studies on other drugs of abuse are almost non-existent.

Researchable questions

The area 'neurobiology of drug abuse' is too vast to be pursued by any single discipline. Each speciality should decide its priority areas of research. It is our suggestion that the following broad areas be given utmost importance:

(a) Tolerance and dependence should be studied involving both animal and human subjects. Substances (agonists and antagonists) with selective affinity to specialized receptors should be used to study reshaping of tolerance and decay of withdrawal symptoms.

(b) Neurotoxicity due to acute and chronic consumption of alcohol is the other major area of concern. Metabolism of ethanol/acetaldehyde can be modified through drugs and these in turn could influence behavioural toxicity and CNS damage.

(c) Many psychotropics are available in India for clinical use and new ones are introduced every year. It is important that these compounds are reassessed for their dependence/abuse liability. Such studies would focus on behavioural psychopharmacology and would include preclinical and clinical experiments. These would lead to rational prescription by clinicians.

(d) Biological vulnerability to drug abuse needs to be studied. Here, FHP subjects should be studied for electrophysiological abnormalities in CNS even before manifest dependence. Electrical activity of the brain associated with drug-induced euphoria should also be examined closely.

(e) Newer imaging techniques (MRI/NMR/PET) should be used to study physiological states of the brain following acute and chronic use.

The following specific issues should be investigated:

(i) *Role of GABA in CNS changes following alcohol consumption*: GABA antagonist/inverse agonist should be closely examined for their role in reversing some of the acute effects of ethanol.

(ii) *Biological and neurochemical basis of craving and pharmacological methods to alleviate this*: As there is no appropriate animal model of craving, such studies would largely require participation of human volunteers.

(iii) *Measurement and quantification of the reinforcing property of various substances*: Such studies would also measure drug discrimination, self-administration and stimulus properties of various compounds.

(iv) *Suppression of activity of various ADH subfractions with the aid of exogenous agents*: Such compounds would be very useful to treat tissue damage due to excess alcohol use and methanol poisoning too.

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