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A pilot study of the kindling hypothesis of dependence on sedative-hypnotic drugs

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SECTION A - Achievements

1. Objectives of research

To establish animal models, and to use them to begin to test aspects of an extended hypothesis which holds that withdrawal from chronic treatment with sedative-hypnotic drugs, including alcohol and benzodiazepines, leads to activation of excitatory mechanisms in the brain, which sensitise (kindle) with repeated experience of withdrawal; this sensitisation process results in an intensification of withdrawal signs and symptoms with repeated withdrawal, and may contribute to relapse and future drug use. Positive results in these studies would pave the way for future investigations of the commonality of the mechanisms underlying withdrawal sensitisation, behavioural sensitisation and drug dependence.

2. Methodology

We employed a progressive ratio schedule to study motivation for ethanol in rats. Although such schedules have been used frequently in animal experimental studies of drugs of abuse, this was the first rigorously defined study of progressive ratio behaviour in animals self-administering ethanol. Although "breaking points" of rats responding on this schedule for ethanol were much lower than those seen in animals responding for psychomotor stimulants, the method promises to be useful in future studies of the effects of pharmacological treatment on motivation to drink ethanol.

3. Scientific Advances

It was demonstrated for the first time that repeated episodes of chronic treatment with a benzodiazepine, diazepam, followed by periods of drug withdrawal sufficient to allow the drug to be eliminated from the system, results in an increased susceptibility to convulsions, when compared to a chronic drug treatment giving a similar total drug load, and exposure, but in which the animals experienced only one period of withdrawal. A similar sensitisation to the anxiety observed in benzodiazepine withdrawal was not seen. In the 12 months time period of the project, it was not possible to investigate changes in brain excitatory systems which are postulated to underlie sensitisation processes, as was originally planned.

Repeated episodes of chronic exposure and withdrawal from alcohol, led to rats showing higher breaking points on a progressive ratio schedule of operant responding for ethanol solution (a measure of motivation to take ethanol, and possibly craving) than animals which did not receive chronic ethanol. Since this increased motivation for ethanol was not seen during early cycles of chronic treatment/withdrawal, such a finding is tentatively in agreement with the prediction that repeated ethanol withdrawal may increase motivation to drink, but it was not possible in the time available to perform the essential control experiments which would allow a stronger interpretation.

4 Implications for improving health

If our observations can be extrapolated to patients,

- The finding that repeated episodes of withdrawal from diazepam induces an increased susceptibility to seizures compared to a single withdrawal from an equivalent drug load emphasises the importance of attempts at withdrawal from sedative hypnotics in patients being successful; relapse to drug taking, and subsequent attempts to withdraw may give rise to withdrawal symptoms of increasing severity.
- For this reason, experience with patients who have on several previous occasions attempted unsuccessfully to cease sedative-hypnotic use, may give an exaggerated impression of the symptoms associated with benzodiazepine withdrawal in individuals attempting to withdraw for the first time.
- Inasmuch as short-acting benzodiazepines may not maintain significant brain receptor occupancies for the whole of the period between doses, these drugs may be more likely to be associated with (unintentional) repeated withdrawal, and may thus give rise to more severe dependence.

5. Efforts to disseminate results to user communities

As a result of discussions of the underlying hypothesis, and current results, pilot studies of the consequences of repeated alcohol withdrawal in alcoholic patients are currently being discussed with clinicians responsible for alcoholic patients in the Brighton NHS Trust, and at the Ticehurst Clinics.

6. Staff Development Training

None

7. Collaborations

In addition to the planned collaboration with the Community Alcohol Project Team of the Brighton NHS Trust, and the local Ticehurst Clinics, we have established a close collaboration with [REDACTED] We have helped [REDACTED] group to set up the alcohol self-administration method using progressive ratio schedules, and this is being used in her current MRC-supported projects. Additionally, [REDACTED] and I have obtained Project Grant support from the MRC for collaborative research into the consequences of ethanol dependence on abuse of other drugs of abuse, using intravenous self-administration techniques we have established in our laboratory with other MRC Project support.

SECTIONS B - Outputs

1) *Publications*

Brown G, Jackson A and Stephens DN

Effect of concurrent alcohol on break points in alcohol self-administering rats.

Behav Pharmacol 7: 11 (abstract)

Brown G, Jackson A and Stephens DN

Effect of concurrent alcohol and its withdrawal on break points in rats self-administering alcohol on a progressive ratio schedule.

NIDA Research Monograph (abstract) (in press)

Ward BO and Stephens DN

Sensitisation to repeated withdrawal from diazepam.

Br J Pharmacol Suppl (in press)

In addition, two full manuscripts have been submitted for publication.

2) *Inventions or patents*

None

3) *Awards or Honours*

None