SOME PHYSIOLOGICAL EFFECTS OF PSYCHOTROPIC DRUGS

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It has become accepted that drugs likely to affect sleep, anxiety, 'arousal', or mood should be investigated using sleep research methods. The waking brain is at the mercy of many unpredictable environmental influences which may be immediately present or brought to the experimental situation in the form of prejudices or worries. On the other hand the sleeping brain offers a period of relative freedom from besetting daytime problems, and techniques now available permit simple measurements of human brain function to be made during sleep.

Patients or volunteers who are used in sleep research have to sacrifice some of their usual comforts to sleep in a laboratory on specified nights, sometimes over a long period. They must abstain from alcohol and preferably from all other drugs for several weeks in advance of and throughout the study. They should lead a regular life, avoiding late nights or other causes of sleep deprivation and sometimes they will be asked not only to undergo electrophysiological recording but to have special procedures conducted, such as all-night venous catheterization. The research workers must provide the equivalent of hotel accommodation. Studies in which venous catheterization is used require the presence of a medical investigator and responsible personnel throughout the night. It is an expensive form of research but there are few others that permit measurements to be made on human brain function.

The measurements

All-night recordings are made of electroencephalogram (EEG), electro-oculogram and submental electromyogram. On the basis of these simultaneous tracings the records are scored into categories of wakefulness, NREM (orthodox) sleep stages 1, 2, 3 and 4 and also into REM (paradoxical) sleep according to widely agreed criteria (Rechtschaffen & Kales, 1968). Naturally it is also possible to record simultaneously other variables such as body movements, EKG, respiration, spontaneous fluctuations of skin potential and so on.

The onset of sleep after lights-out is usually taken from the first stage 2 with its characteristic spindles of about 12-14 Hz and high voltage slow wave complexes. The recording paper is run during the night at a speed of 15 mm/s which means that individual

pages represent 20 s each and it is these that form the units of measurement. The all-night records are scored by eye and hand and, contrary to what some people suppose, this is not a particularly time-consuming task compared with all the other work of the night's recording.

Each change of stage is recorded by its page number on a proforma and the data then transferred to punched cards, after which a suitable computer programme converts the scores into data convenient for final analysis.

Sleep duration and latency

The total duration of sleep may be decreased by amphetamine derivatives (Lewis, 1970) or increased by hypnotics but on the whole it is not a particularly valuable measure, partly because of the very high variance usually found. Often the only effect that may be seen is a reduction of sleep after withdrawal of hypnotics or similar drugs. The time taken first to fall asleep after lights-out is similarly a rather poor measure because there are sometimes technical delays in getting subjects to bed and then finally to the point of lights-out.

Here, too, there is often a large variance that makes it difficult to achieve a significant result. One is faced with the practical dilemma of whether to give the drug an hour before bedtime (a bad clinical practice) in order to try to demonstrate a shortening of sleep latency or whether to give the drug at bedtime (a better clinical practice) and thus give insufficient time for the drug to be having much effect before the likely mean time for falling asleep.

The EEG rhythms

A drug can alter the EEG rhythms themselves. Such drugs as barbiturates and nitrazepam cause fast rhythms of about 18 Hz which are superimposed on the other EEG rhythms, are most marked over the front of the head, and seen primarily in drowsiness and in REM sleep (Oswald, 1968). It is a feature that can indicate the persistence of clinical doses of drugs for longer than might have been expected but it may be missed unless the EEG recordings are made without the usual high-frequency filters. The normal

Figure 1 Caffeine makes sleep more broken. Cumulative amounts of intervening wakefulness and drowsiness are higher after caffeine (300 mg) (●—●) than after decaffeinated coffee (■—■), or no drink (○—○) before sleep. Data from six late middle age subjects, 15 nights each, in the study by Březinová (1974).

12–14 Hz sleep spindles are enhanced in amplitude and duration with some of the benzodiazepines and with tricyclic antidepressants.

Broken sleep

The degree to which sleep is broken is a useful measure. One may determine the number of minutes of wakefulness that intrude in the process of accumulating, say, 6 h of sleep and may perhaps add to this the amount of time spent in drowsiness (stage 1) so that Figure 1 shows an example of one of the commonest of psychoactive drugs, namely caffeine, increasing the degree to which sleep is broken following a dose equivalent to two cups of coffee at bedtime (Březinová, 1974). Another approach is to measure actual body movements, though these have become unpopular because of their poor discriminative value compared with the EEG stage transitions. If one looks simply at the number of transitions into stage 1 or wakefulness per unit time of accumulated sleep, one finds increases from such drugs as amphetamine derivatives, imipramine and

chlorimipramine (Dunleavy *et al.*, 1972) or after withdrawal of many hypnotic or anti-anxiety drugs (Oswald *et al.*, 1973).

The opposite effect of reduction in the degree to which sleep is broken can be seen with administration of most hypnotic and anti-anxiety drugs and has also been observed as part of the withdrawal reaction following amphetamine derivatives (Lewis *et al.*, 1971).

REM sleep

REM sleep duration has been much studied and is reduced by most drugs which act on the human brain. A few increase REM sleep duration, for example, reserpine (Hartmann, 1966; Hoffman & Domino, 1969). A few years ago it was tempting to predict that any drug that might affect monoamine mechanisms and that enters the human brain would reveal effects on REM sleep. However, a study of a drug used as an anti-anxiety agent, namely propranolol 120 mg at bedtime, failed to reveal any effect on sleep or any blocking of the powerful actions of dexamphetamine or imipramine (Dunleavy *et al.*, 1971). This rather disappointing result with a β -adrenergic blocking agent, however, prompted studies of an α -adrenergic blocking agent, thymoxamine, and led to the finding that intravenous thymoxamine during sleep caused a very striking increase in REM sleep duration, leading to the conclusion that there are α -adrenergic receptors in the human brain and that it is these that are involved in the control of sleep (Oswald *et al.*, 1974).

Phenothiazine drugs, notably mesoridazine, can also increase REM sleep duration and the effect of phenothiazines in blocking adrenergic input enables them to be seen in a light similar to thymoxamine.

Drugs that elevate mood are outstandingly powerful in reducing REM sleep duration—the amphetamines, drugs like imipramine, and the MAOIs. In the case of the MAOIs there can be total abolition of all signs of REM sleep, but this occurs only after the use for a week or more of doses such as phenelzine 75 mg. Not all depressed patients respond to the MAOIs but, in those who do respond, the delayed response begins at the same time as the delayed abolition of the signs of REM sleep (Dunleavy & Oswald, 1973). It is of interest that Vogel *et al.* (1974) have now accumulated a large series of patients in a double blind clinical trial whose depression has been relieved by the behavioural suppression of REM sleep through selective nocturnal awakenings.

At one time it was proposed that loss of REM sleep would have dreadful consequences for the psyche (Fisher & Dement, 1963) but this can no longer be sustained. It may be of course that whatever benefit is brought to us during REM sleep is in some way substituted for by the MAOI drug. In any case the brain is wonderfully adaptive and what it cannot

achieve in some usual and optimal way it usually achieves in some other way.

At the present time it seems likely that REM sleep in natural circumstances is especially important for synthetic processes in the brain. The large brain blood flow at this time is clearly directed to inner needs and not to enabling the brain to cope with the outside world, but it must be said that reduction of REM sleep by drugs has not yet been shown to be harmful, even though one might argue that the less distorted the natural rhythms of sleep are after a drug the better.

Slow wave sleep

The slow wave stages of sleep known as stages 3 and 4 have attracted much more interest in the past few years and one reason for this has been the fact that they are linked in time with the principal secretion of growth hormone during the 24 h and also appear to be especially related to bodily restorative needs. Thus they are increased in conditions where the tissue reserves have been burnt up at a fast rate on account of acute starvation, hyperthyroidism or possibly extra physical exercise, and in all these instances there is evidence of an associated increase in the secretion of nocturnal growth hormone. Stages 3 and 4 of sleep are reduced in duration by some of the benzodiazepine drugs, notably flurazepam (Kales *et al.*, 1970a; 1970b).

Distribution through the night

It is important not only to look at the amount of some normal feature of sleep in, let us say, the first 6 h of sleep, but also to look at the distribution through the night of that stage of sleep or of transitions between stages. Thus an amphetamine derivative may lead to a suppression of REM sleep in the early night with an intra-night rebound in the later hours of sleep. The effect on the whole night may seem nil, and not until one looks at the hour by hour distribution of sleep stages does the action of the drug become apparent (Oswald, 1970). Similarly when sodium amylobarbitone has been used over a long period of time it still diminishes the extent to which sleep is broken in the early night, but in the later night sleep is more broken than it would have been if the drug had not been taken (Ogunremi *et al.*, 1973). Even before the war, that most common of psychoactive drugs, alcohol, was found to have this effect of diminishing restlessness in the early night but increasing it in the late night following an evening drink (Mullin *et al.*, 1933).

The necessity for chronic studies

One of the things that we have learned by experience is that single-dose studies of a drug give an incomplete answer and sometimes a misleading one. In clinical practice, psychoactive drugs are taken over long

periods and it is therefore desirable that studies of their effects on human feelings and functions should be conducted over periods of weeks.

The first dose of an MAOI may have hardly any effect but repeated dosage leads after 1 or 2 weeks to dramatic effects. Flurazepam 30 mg has no effect on stage 4 sleep at first but after 2 weeks of use suppresses it as already mentioned. In a study of the effects of single doses of fenfluramine on sleep no action of the drug was found (Oswald *et al.*, 1968) but this was because the drug, as was later realized, is normally a cumulative drug, the concentration of which in the tissues gradually builds up over a period of days and when chronic studies were later undertaken fenfluramine was found to have many actions on the brain, with rebound abnormalities on withdrawal (Lewis *et al.*, 1971).

Rebounds

Conventional drug experiments involving single doses of varying size, in some neat design in which placebo is included, are readily susceptible to statistical evaluation. Unfortunately they make the incorrect assumption that rebounds do not exist and they bear no relation to the normal clinical administration of psycho-active drugs. Rebound abnormalities in sleep are seen when a drug is withdrawn and placebos substituted. A drug that reduces REM sleep duration leads to rebound increase after its withdrawal. A drug that diminishes restlessness during the night leads to increase of restlessness above normal when the drug is withdrawn. Whether or not rebounds of slow wave sleep stages 3 and 4 ever occur are, however, doubtful. Rebound effects can be shown to last for periods of 4–7 weeks, from which one may conclude that the previous presence of the drug caused some modification of brain constituents and that these modifications had a life span of the order of a month or so, as might be judged from their rate of decay.

The time to the peak of the REM sleep rebound is roughly related to the time taken to eliminate the drug and can be 4 days after fenfluramine (Lewis *et al.*, 1971), 3 weeks after a very large dose of phenobarbitone that takes 3 weeks to eliminate (Haider & Oswald, 1970), 10 days after heroin when a similar period is needed to clear products from the urine (Lewis *et al.*, 1970) and similar time relations have been observed with nitrazepam overdose (Haider & Oswald, 1970) and after large doses of tricyclic drugs (Lewis & Oswald, 1969).

The physiological indices affected in the withdrawal rebound are commonly paralleled by psychological rebound phenomena which can be measured contemporaneously. Thus withdrawal of fenfluramine leads to depression of mood, maximal 4 days after stopping the drug, and withdrawal of anti-anxiety drugs leads to a few days of anxiety, poor concentration (Ogunremi *et al.*, 1973) and to nightmares.

Blood sampling

In the past few years it has become known that growth hormone, prolactin and (in early puberty only) luteinizing hormone are secreted in large amounts during sleep, the secretion being dependent on sleep for its occurrence. In many laboratories, techniques have been evolved for withdrawing blood without disturbing the sleeping subject. Sampling at intervals of 15–30 min with separation of the plasma, deep freezing and subsequent assays conducted blind for the conditions, is leading to reports of a new area of research.

It has been observed that the withdrawal of the anti-anxiety drugs sodium amylobarbitone and benzocetamine leads to a temporary rise in the nocturnal growth hormone secretion (Ogunremi *et al.*, 1973). Plasma corticosteroids, often taken as an index of stress, are found to be diminished in sleep during the weeks of intake of an anti-anxiety drug and are significantly increased above normal in the first week after withdrawal of the anti-anxiety drug (Ogunremi *et al.*, 1973). In experiments of this nature one may plot graphically the plasma concentrations at different times of the night and then measure the area under the curve between chosen periods of the night and compare the areas for the differing conditions.

It has to be said again that research of this nature is expensive and that consequently unless a drug is regarded as of major importance only a few subjects

or patients are likely to be studied. Their small numbers militate against dose-response studies, and both the small numbers and the gradual evolution of effects across time do not suit conventional statistical methods. Chronic studies with only a few subjects nevertheless permit the demonstration of consistent patterns of response over time and do not preclude simple calculations of probability. If one has, say, studied only three subjects for some 60 nights each and has predicted that their lowest REM sleep percentages would occur in the first drug week and that their highest would occur in the first withdrawal week, and if it is found that the three lowest and the three highest values for each man occur in the predicted weeks then statistics can be superfluous.

Conclusion

Sleep research is a tool for chronic studies of the human pharmacology of psychoactive drugs. It gives information about initial drug effects, about tolerance, about late drug effects and about withdrawal phenomena. The studies may be combined with behavioural and psychological measures which may also reflect the changing pattern of the drug's action with the weeks and may also be combined with studies of blood constituents such as hormones. The methods are expensive and best suited to detailed investigation of intra-sleep features in small numbers of subjects (Oswald, 1973).

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