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An analysis of the learning deficit following hyoscine administration to man

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Summary

1. Twelve volunteer subjects completed a free-recall word learning test, a number-colour association test, and a scanning task after the following treatments: saline 1 ml, hyoscine 0·4 mg, or atropine 0·6 mg, administered by intravenous injection.

2. Performance on all three tests was not significantly impaired after atropine.

3. Performance on the two learning tests but not on the scanning task, was significantly impaired after hyoscine.

4. Analysis of the results of the free-recall word learning test indicates that impairment of learning following hyoscine does not affect recall over intervals of a few seconds, but affects that portion of the learning curve which has been attributed to long-term (or secondary) rather than short-term (or primary) memory.

5. The results suggest that hyoscine 0·4 mg may impair learning processes, without significantly depressing other psychological functions, and that the impairment of learning following hyposcine does not affect recall over intervals memory.

Introduction

Interest in the effects of drugs on learning processes dates from Gauss' (1906) description of 'twilight sleep' following the use of morphine and hyoscine in labour. The concept of a state in which the subject is conscious to the extent of reacting appropriately to sensory stimuli yet for which no memory trace is formed implies that the action of the drugs involved is at least relatively selective for learning as opposed to other psychological processes.

Recently attention has focussed on the amnesic properties of hyoscine when the drug is used as a pre-medicant for anaesthesia. Hardy & Wakely (1962) found a 13% incidence of amnesia for a simple visual stimulus following hyoscine pre-medication as compared to 1% incidence following atropine, using standard clinical doses of either drug. Pandit & Dundee (1970) found a significantly increased incidence of amnesia for events preceding induction of anaesthesia in subjects treated with hyoscine and hyoscine-diazepam mixtures; and Pandit, Dundee & Keilty (1971) showed that diazepam 10 mg, and hyoscine 0·4 mg administered either separately or in combination caused significant amnesia as assessed by the recall of events preceding anaesthesia, and by a colour naming task. However, both drugs caused a degree of sedation by comparison with

saline. Frumin, Herekar & Jarvik (1969) presented similar findings and attempted to control for the possibility that sedation contributed to the result by re-testing the subjects 1 min after presentation of the test material. Of the subjects performing correctly at this time a higher proportion of those treated with diazepam/hyoscine mixtures showed impaired recall at 24 hours.

These studies suggest that small doses of drugs such as hyoscine and diazepam exert an action on learning processes, albeit a small one, and that this effect may not necessarily be attributable to a general depression of cognitive function.

Studies on human learning suggest that two separate stages may be involved; short-term, or primary, and long-term, or secondary, memory (for recent reviews see Broadbent, 1970; Craik, 1971; Baddeley & Patterson, 1971). This dichotomy can be conveniently studied by the use of a free-recall task (Glanzer & Cunitz, 1966; Baddeley & Warrington, 1970). In the present experiments two learning tests (a free-recall task, and a colour-number association test) and a scanning task were used in an attempt to determine whether standard clinical doses of atropine and hyoscine have effects on learning processes separable from their effects on general psychological functioning. If such an effect could be demonstrated it was hoped to determine whether long-, or both short- and long-term memory were affected.

A preliminary account of these experiments has appeared (Crow & Grove-White, 1971).

Methods

Subjects

12 medical students (10 males, 2 females; age range 19–23 years) volunteered and were paid to act as subjects in each of 3 sessions.

Subjects were seated in groups of 3–4 within a sound-proof chamber and each subject was provided with a pair of headphones and writing rest. Test material, including the instructions, was presented to the subjects from a tape record.

Experimental design

All subjects were submitted to the battery of tests on each of 3 occasions, receiving either hyoscine, atropine, or saline 5 min before the beginning of the test. Three sets of test material (see below) were used and the order of drug treatments was such that in one test session each treatment was administered to 4 of the subjects in a balanced design. The drugs were administered intravenously in the following dosages: (−)-hyoscine 0·4 mg in 1 ml; atropine 0·6 mg in 1 ml; sodium chloride injection 1 ml.

Neither the subjects nor the experimenter administering the psychological tests were aware of which of the treatments the subjects had received.

Psychological tests

Two tests of learning capacity, a free-recall and a number-colour association test, and a scanning task were administered. The material of the number-colour association test was presented before the free-recall and scanning tasks, and testing took place after these tests had been completed. The free-recall and scanning tasks were administered together as described below.

(i) *Number colour associations.* Subjects were required to memorize associations between the digits 1–7 and particular colours after having these associations presented to them three times. They were asked to write these associations down at the end of the free-recall test (i.e. 25 min after first memorizing them).

(ii) *Free-recall test.* In each test session subjects were required to memorize 10 lists of 10 words presented to them at a rate of 1 word/3 seconds. The words selected were of 2–3 syllables with a frequency of occurrence of less than 15 per 100,000 words (Thorndike & Lorge 1944). Subjects were permitted to recall and record the words in any order. In alternate lists they did this, either directly after presentation (immediate recall) or after 64 s of an interpolated scanning task (delayed recall).

(iii) *Scanning task.* This test was inserted in the 64 s interval between registration and recall in the 'delayed recall' parts of the free-recall test. Subjects were presented with sequences of alphabetical letters at a rate of 1 letter/s, and required to detect and record whenever two alphabetically successive letters (ab, xy, etc.) occurred successively in the sequence. The letter sequences were generated by a computer programme incorporating a 'pseudo-random' number generator. Particular sequences were selected to give a mean number of 5 positive signals in each 64 s interval (i.e. a maximum score of 25 in one test session). The test had two functions—to prevent rehearsal of the 10-word list during the 64 s delay and to provide a measure of cognitive function with a minimal component of learning.

Results

Subjects' performance following hyoscine administration was significantly impaired on each of the tests involving a component of learning: the immediate- and delayed-recall parts of the free-recall test, and the number-colour association test (Table 1). There was no significant impairment on any of these tests following atropine administration. There was no impairment in performance on the scanning task after either atropine or hyoscine administration.

The results of the free-recall test can be analysed by order of presentation of words within the 10-word list. When this is done (Fig. 1) a well-marked 'recency effect' (see **Discussion**) emerges in the immediate recall part of the test. The decrement in subjects' performance after hyoscine does not affect this part of the curve but is present in the remaining segment of the immediate recall curve and in the delayed recall part of the test.

Most subjects complained of experiencing dryness of the mouth after both atropine and hyoscine. Spontaneous reports of other subjective sensations were

TABLE 1. *Subjects' performance after saline, hyoscine* 0·4 *mg, and atropine* 0·6 *mg on three tests with a learning component and a vigilance task*

	Immediate recall	Delayed recall	Number-colour associations	Scanning task
Maximum score	50	50	7	25
	Mean correct responses ±1 S.E.M.			
Saline	27·9±1·6	14·3±1·3	7±0	22·3±1·2
Hyoscine	24·0±1·3*	10·2±1·3**	5·9±0·5*	20·5±1·1
Atropine	25·9±1·3	14·1±1·7	6·9±0·1	20·3±1·2

* $0{\cdot}05>P>0{\cdot}01$; ** $0{\cdot}001>P$ vs. saline.

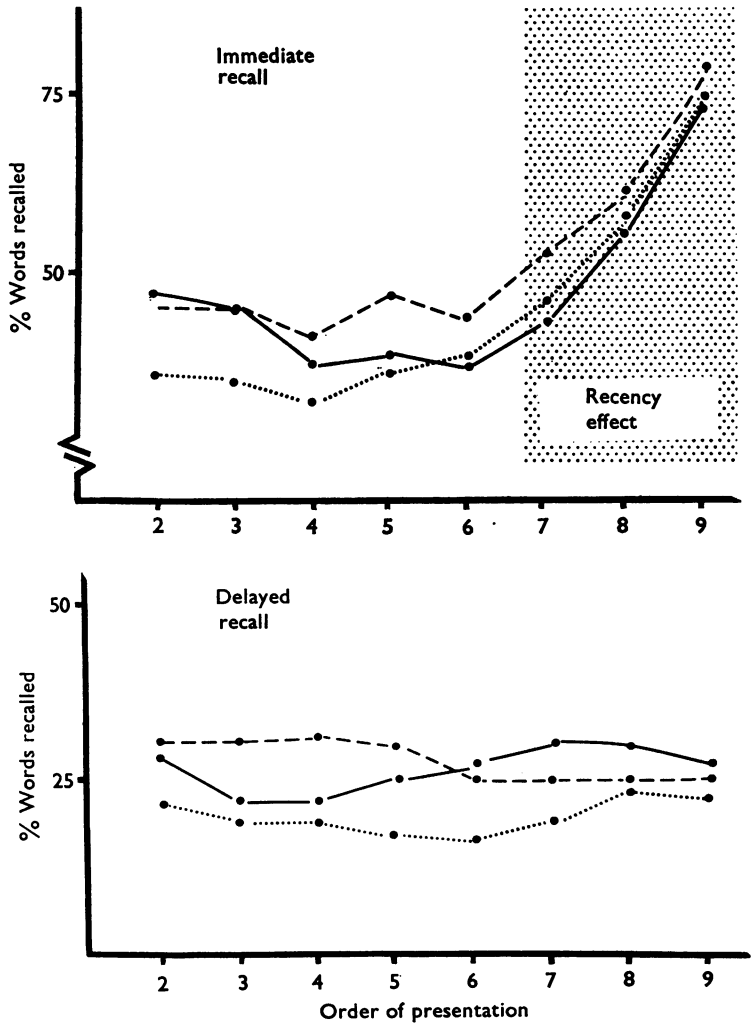

FIG. 1 An analysis of free-recall test results by order of presentation of words within the 10-word list (running totals, averaged over 3 positions-at-a-time). There is a well marked 'recency effect' (see **Discussion**) in the immediate recall, but not in the delayed recall, condition (saline 1 ml - - - - - - - ; atropine 0·6 mg ——— ; hyoscine 0·4 mg .....).

infrequent but two subjects mentioned feeling 'light-headed' and 'dizzy' after hyoscine.

Discussion

The results show that doses of hyoscine which have been reported to produce amnesic effects in clinical situations (Lambrechts & Parkhouse, 1961; Pandit & Dundee, 1970) can be demonstrated to have significant effects on simple tests of human learning capacity.

The impairment following hyoscine 0·4 mg did not occur after atropine 0·6 mg. It is generally recognized that the central effects of atropine occur at higher dose levels than those at which central effects are observed following hyoscine (Longo,

1966). The time-course of the action of the two drugs may also differ, but comparisons of their peripheral actions (Herxheimer, 1958) suggest that the differences are relatively small.

Hyoscine 0·4 mg impaired performance on the learning tasks (free-recall and number-colour association tests) but did not impair scanning task performance. The effect of hyoscine does not therefore appear to be to produce a general depression of higher nervous activity, and may possibly be relatively selective to learning function.

There is now considerable evidence (Broadbent, 1970 ; Craik, 1971) that registration and recall processes over very short intervals (of a few seconds) have quite different characteristics from learning processes operating over longer recall intervals. On the basis of such findings it has been suggested (e.g. Waugh & Norman, 1965) that two stages in the learning process can be distinguished: short-term (or primary) memory, and long-term (or secondary) memory. Amongst the methods available for distinguishing between these stages is the free-recall technique of Glanzer & Cunitz (1966). When subjects are asked to recall a list of 10 words immediately after they have heard the list recited, the last words in the list are much better recalled (the ' recency effect ') than those earlier in the list. Since this effect disappears when recall is delayed by the interposition of another task between presentation of the list and recall, it is argued that the ' recency effect ' reflects the operation of the short-term memory mechanism.

In the present experiments impairment of learning following hyoscine does not affect the part of the free-recall curve attributed to short-term, or primary, memory (Figure 1). Rather, it falls evenly on those parts of the curve attributed to longer-term storage.

The learning deficit following hyoscine is identical in form to, though of lesser magnitude than, that demonstrated by Baddeley & Warrington (1970) in patients with a memory defect of the type seen in Korsakow's psychosis. Baddeley & Warrington (1970) used a battery of tests to distinguish short- from longer-term memory and found that a free-recall test discriminated the patients from the controls on the long- but not on the short-term component. The defect in either case seems to be at the point of transfer of information from a short-term store into a more durable state.

Whatever the precise mechanism the present findings may perhaps be taken as further evidence for a distinction between two stages in the human learning processes, and may possibly reflect on the neurohumoural mechanism involved in the transition between these two stages. There is suggestive (Brierley, 1966), but not conclusive (Adams, 1969) evidence that lesions of the hippocampo-mammillo-thalamic circuit play a causal role in the genesis of Korsakow amnesia ; it seems possible that hyoscine exerts its action at some point in this neural system.

The distinction between short- and long-term memory components based on analysis of the free-recall test is relevant to the phenomena of Korsakow's psychosis (Baddeley & Warrington, 1970) and to the amnesic actions of hyoscine (present results) but it should be noted that it does not correspond to some other dichotomies of the learning process. Learning can be disrupted by electro-convulsive therapy (E.C.T.) (Cronholm, 1969), by head injury (Russell, 1971) and, in animal experiments, by protein synthesis inhibition (Barondes, 1969). Resistance to these latter agents develops slowly over a time-course of hours from the original learning

experience. The process underlying this change, sometimes referred to as 'consolidation', marks a transition from an 'intermediate' store (of a few hours' duration) to a very long-term type of storage. Any dichotomy of the learning process based upon the effects of E.C.T., head injury or protein synthesis inhibition therefore is quite separate from the distinction between short- (a few seconds) and long-term memory processes studied in the present experiments.

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