Psychopharmacologia 3, 193—201 (1962)

From the Institute of Psychiatry, Maudsley Hospital, London, S.E.5

An Investigation of Drug Induced Sensory Disturbances

By

F. S. MORGENSTERN*, H. R. BEECH and B. M. DAVIES

(Received March 5, 1962)

Introduction

While there have been many descriptions of the symptoms produced by various psychotomimetic drugs, there are relatively few objective studies of the way in which these drugs modify various aspects of normal psychological functioning. Such investigations would clearly be helpful not only in gaining knowledge of the mechanisms underlying the disruptive influences of these drugs, but also in understanding something of the processes underlying mental disturbances.

One of these drugs, phencyclidine (a synthetic cyclohexylamine derivative previously known as sernyl) was introduced into anaesthetic practice (GREIFFENSTEIN et al.) because of its ability to produce analgesia without loss of consciousness. Post-operatively, however, psychiatric disturbances were common, and the use of the drug in anaesthetic practice has since been limited. The psychological dysfunctions produced by this drug have been investigated by psychiatric workers, such as LUBY et al. and DAVIES and BEECH, with interesting results. It has been suggested that the drug acts mainly at the thalamic level (GREIFFENSTEIN et al.), producing changes in reception of sensory stimuli, but in addition there are disturbances in cognitive functioning which superficially resemble those found in thought-disordered schizophrenics.

The relationship between the sensory disturbances on the one hand and the thinking difficulties on the other is not clear, but is has been suggested that the drug may produce some of its psychological effects by creating a state of internal sensory deprivation (BEECH et al.). In a preliminary communication (BEECH et al.) the argument was put forward that if alterations in the balance of input of sensory information are capable of producing disturbances characteristic of schizophrenia (BEECH et al.), the subjects under the influence of phencyclidine might also be expected to produce such symptoms, as its action serves to limit the amount of available sensory information (BEXTON et al., EDWARDS and COHEN; MENDELSON and FOLEY). In our initial experiments (BEECH et al.) it was clear that while cognitive dysfunctions accompanied the

* Working under a grant from the National Institutes of Health of America, no. MY-2612 (C 2) PMY (5).

administration of the drug, these changes did not appear to be like those found in the thought: disordered schizophrenic patient. However, it was still possible that the disruption of normal thinking processes could be attributed to sensory changes and our preliminary experiment led us to believe that the latter would make an appropriate avenue of further inquiry.

The present experiment was therefore undertaken in order to develop the observations made in our earlier study respecting alterations in sensory thresholds concomitant with the administration of phencyclidine. In particular we were interested first in broadening the scope of our investigation by examining the effects of the drug upon more than one modality. Secondly we were interested in carrying out continuous measurements of the effects of this drug upon sensory functioning throughout its course of action. Thirdly, we were interested in any information which we might obtain concerning the hypothesis advanced in an earlier paper (BEECH et al.), namely that the changes in sensory threshold actually produced the cognitive disturbances noted.

Material and Methods

Subjects. The subjects used for this investigation were 18 healthy volunteers between the ages of 20 and 40 years; most of them had professional occupations. Subjects were only included in the study if there was no evidence of serious past or present mental, or physical illness, and if they were not in the habit of taking drugs of any kind. None had taken medication of any sort during the week preceding the tests. All subjects were instructed to take only a light breakfast before the tests. Six control subjects were tested for two consecutive hours: the twelve experimental subjects were tested continuously until their test performance had returned to near normal.

Methods. When the nature of the tests had been explained to the subject, 7.5 mg of phencyclidine was given in the form of tablet or cachet, followed by a glass of water. Testing began at once. Sensory thresholds were obtained on a battery of seven tests. This battery was administered every fifteen minutes, and took ten to twelve minutes to complete. The individual tests were of perimetry, visual acuity, auditory theshold, taste threshold, touch and two point discrimination thresholds, and position sense.

Perimetry. A Goldman spherical projection type instrument was used, in which bowl and target lighting are derived from the same source, and the target is moved by a stereotactic device controlled from the back of the instrument. The relative intensity of the bowl and target light used was 1:10 and the area of the target, 64 mm^2. Measurements were along one axis (horizontal) only, and judgements

were recorded when the light disappeared and reappeared at the periphery. Each reading used in the analysis of the results represents the average of sixteen such judgements. Units are in millimeters from the extreme periphery of the field (at 0 mm).

Audiometry. The auditory stimulus was provided by an A. F. Generator — type H model 1, the frequency used being 2000 c.p.s., for all subjects. The intensity of the tone was controlled by a potentiometer, and delivered to the subject through ear phones. Units are arbitrary divisions on the potentiometer representing equal changes in resistance.

Visual acuity. This was tested with a Snellen Chart using the Landolt rings. The measure of acuity was the number of correct responses to 10 presentations of figures at the limit of acuity before taking the drug.

Taste thresholds. These were measured in terms of the least concentration of Quinine sulphate which the subject could discern clearly, out of an array of six different strengths: 0.1, 0.05, 0.01, 0.005, 0.001 and 0.0005%, and distilled water, labelled 1—6 in that order, for purposes of measurement. The liquid was applied to the tongue by a glass rod which had been dipped in the solution. The rods were cleaned after each trial, and the subject washed his mouth with water between trials.

Touch. Thresholds were assessed with a v. FREY hair. A spot marked in ink on the right thenar eminence was used for each determination.

Two-point discrimination. A pair of dividers was applied to a line drawn on the thenar eminence of the right hand. Judgements of the transition from one to two points and again from two to one point were recorded in millimeters, and their average value taken as the threshold.

Position sense. The measure used was the number of correct judgements out of ten, of the direction in which the distal interphalangeal joint of the right index finger was moved.

Results

Basing our hypothesis upon results obtained in our previous experiment it was predicted that interference with peripheral-somatic sensitivity (e.g. raising touch and pain thresholds) would produce lowered thresholds in other modalities (e.g. vision and audition). It should therefore follow that our experimental group should show a deterioration (raised threshold) for perception of two-point discrimination, aesthesiometry, and position sense, and an improvement (lowered threshold) for perimetry, visual acuity, audiometry, and taste, following administration of the drug. Our control group, on the other hand would be expected to show either no changes or lowering of thresholds consistent with practice effects.

It will be appreciated from the results presented in Table 1 that our predictions in respect of the performance of the experimental group on tests of taste, perimetry, visual acuity, and audition, are negated. Over the first two hours of testing the experimental group showed a consistent decline in performance in all modalities, i.e., generally raised thresholds are characteristically produced by this drug. On the other hand the control subjects showed either no change or an improvement in performance (lowered thresholds) on all tests and modalities.

Table 1. *The change scores on which the threshold trends reported in the above table were based were obtained by subtracting the average deviation in threshold readings over the first 2 hours of testing from the initial threshold score*

Test	Experimental group		Control group	
		Change score		Change score
Primetry	d	+13.8	i	−27.5
Audiometry . .	d	+ 7.7	i	− 1.9
Visual acuity . .	d	− 8.2	i	+ 4.7
Two-point discrimination	d	+24.1	i	− 7.5
Aesthesiometry .	d	−16.4	i	+ 1.0
Position sense .	d	− 8.0	s	0.0
Taste	d	− 3.4	i	+ 3.7

d=raised threshold, i=lowered threshold; s=no change. Units of measurement, as deserибed under 'methods'.

Not only was it the case that our experimental subjects differed from the controls in terms of the direction of "change" scores (thresholds being raised for the former group and lowered for the latter group), but also the variance of the change scores over the first two hours of testing tended to be significantly greater for the experimental group than for controls. The relevant statistical data showing these trends are given in Table 2.

At this stage it seemed reasonable to argue that, contrary to our expectations the drug phencyclidine appears to produce a general

Table 2. *The figures under 'Experimental Group' and 'Control Group' refer to standard deviations of threshold measurements over the first two hours of testing*

Test	Experimental group	Control group	F-ratio	Sig.
Perimetry	2.97	2.37	1.57	n. s.
Audiometry	0.70	0.32	4.90	0.05
Visial acuity	0.89	0.74	13.10	0.01
Two-point discrimination. . . .	2.60	0.45	33.80	0.001
Aesthesiometry	1.27	0.46	7.87	0.05
Position sense	0.87	0.00	Inf.	0.001
Taste	0.43	0.24	2.00	n. s.

impairment in sensory functioning not confined to peripheral somatic sensitivity. It now becomes pertinent to ask whether there is a tendency for certain functions to be affected more than others in all subjects.

This possibility was examined by ranking the performance of subjects on the various tests according to the size of the 'change' score, calculated as shown in Table 1. If for Subject I, for example, visual acuity had been the highest 'change' score, then this test would be given a rank of 1 for this subject, the test with the next highest 'change' score being rank 2, and so on. These ranks were then treated as scores and an analysis of variance was carried out on them. Should there be a tendency for one test to produce higher (or lower) rankings than another, then this would be reflected in a significant F-ratio for the 'tests' main effect. The F-ratio was in fact significant at beyond the 0.001 level.

Table 3.
Ranking according to size of change score

Test	Average ranking for all experimental subjects
Two-point discrimination	2.0
Aesthesiometry	3.0
Perimetry	4.4
Audiometry	4.6
Position sense	4.7
Taste	4.8
Visual acuity.	4.9

We may then conclude that the order in which the functions tested are affected by the drug is significant. The actual magnitude of the effects on the various functions are given by the average ranking, for all subjects, of size of 'change' scores. These data are given in Table 3.

From the results given in Table 3 it would appear that, as expected, 2-point discrimination and aesthesiometry are most affected by the drug. All other functions appear to be affected to about the same degree, there being little differentiation in rank order, only 0.5 rank separating the five tests.

A further important consideration is, of course, the relationship between the subjective psychological experiences of the subject influenced by the drug and the sensory changes which are occurring. We have argued that certain of these psychological effects could be attributed directly to modifications in sensory input produced by the drug, and this possibility appears to be strengthened rather than weakened by the findings reported in this paper, namely, that phencyclidine produces general sensory impairment. Naturally a critical issue here will centre around whether or not measurable sensory changes precede the production of psychological effects — although it is recognised that the order in which functions are disturbed (sensory and psychological) does not establish causality.

The method adopted for investigating the relation between the onset of psychological and sensory changes was relatively crude, simply consisting of a comparison between noticeable deviations of threshold

from the starting point and verbal reports of subjective change obtained during testing. In almost every case the first verbal report of psychological change was of a feeling of 'lightheadedness', 'a slightly drunken feeling', a feeling of 'happiness' or of 'being giggly', and this kind of statement was taken to indicate an alteration in psychological state attributable to the drug. Table 4 shows what changes in sensory functioning, if any, had occurred at the time when the first psychological reactions were noted.

Table 4. *Sensory changes at time of onset of psychological changes*

Subject	Perimetry	Audiometry	Vis. acuity	2-pt. disc.	Aes.	P. S.	Taste
1	+	+	0	+	—	0	0
2	+	—	—	—	—	0	+
3	+	+	0	—	—	0	+
4	+	+	0	—	+	0	—
5	+	+	0	+	—	0	—
6	+	—	—	—	—	—	—
7	—	—	0	0	—	0	0
8	+	—	+	—	+	—	+
9	—	—	0	+	—	0	—
10	+	—	—	—	0	0	—
11	+	—	—	—	0	0	—
12	+	—	0	—	—	0	+
Average	+0.67	−0.33	−0.25	−0.42	−0.50	−0.16	−0.16

(These averages are calculated by allocating a score of +1 for each plus sign, a score of —1 for each minus sign and no score for each zero sign.)

+ Improvement compared with first score; 0 no change compared with first score; — impairment compared with first score.

At first sight some of the data reported above may seem to be at variance with what has been reported earlier as a consistent and progressive decline in sensory functioning for all subjects. This statement was based upon an overall evaluation of the first two hours of testing, but initially a moderate trend was noted in experimental subjects to improve their scores, presumably as a result of practice. It is clear, however, from Table 4 that at the time when the first psychological reactions were being reported, most subjects were already showing impairment of sensory thresholds. A notable exception to this occurs in the case of the visual perimetry results, but the trend appears to warrant the conclusion that sensory impairment in general precedes psychological effects. Such an outcome is entirely consistent with our hypothesis that the psychological effects are produced by the sensory disturbances, but this does not, of course, constitute conclusive evidence that this is the case.

The above conclusion respecting the temporal relationship between sensory disturbances and psychological disturbance, is further borne out by an examination of the stages at which these disturbances become maximal. Table 5 indicates that for perimetry, audiometry, visual acuity, position sense, and taste threshold, the maximum disturbance occurs well in advance of the maximum psychological effects.

Table 5. *Average number of minutes elapsing between maximal sensory and psychological effects*

Perimetry	+13.7
Audiometry	+28.7
Visual acuity	+23.5
Two-point discrimination	− 8.1
Aesthesiometry	− 3.7
Position sense	+25.0
Taste	+42.0

+ Indicates that the sensory effects preceded the psychological; − indicates that the psychological effects preceded the sensory.

It will be appreciated, however, from the data given in Table 5, that the decrement in two-point discrimination and aesthesiometry is continuing for a few minutes after the point of main psychological disturbance has been reached. These data, together with those presented in Table 3, suggest that the most pronounced and persistent sensory effect occurs in the case of peripheral and somatic sensitivity, a result entirely consistent with the history and development of the drug.

Discussion

The experiment reported in this paper represents an attempt to investigate the disturbances attributable to the drug phencyclidine systematically, by objective experimental procedures. In the opinion of the authors such studies serve not only to elucidate the mechanisms and action of drugs, but also serve to correct impressions gained from the usual kind of clinical trial where subjective procedures take precedence over precise measurement and control. Our researches have, in fact, led us to conclude that, at least in one respect, the drug phencyclidine does not replicate the symptoms of psychosis, namely 'thought disorder'. However, our investigations have indicated a number of phenomena deserving closer attention and requiring explanation, and the theory has been propounded that the psychological disturbance produced by the drug could, at least in part, be attributed to the sensory disturbances which accompany its administration.

While our initial studies suggested that some process of sensory facilitation might be produced by the direct action of phencyclidine upon peripheral-somatic sensitivity, the investigation reported in the present paper forces us to the opposite conclusion. The more systematic and detailed investigation carried out in this later experiment in fact leaves no room for doubt that the drug produces general sensory impair-

ment. As our control subjects showed increased sensitivity in the form of lowered thresholds of perception (consistent with practice), it seems reasonable to argue that without practice effects, the degree of sensory impairment noted in our experimental subjects may have been even more profound.

It also appears from the results of the present experiment that there is some kind of lawfulness about the action of the drug in the sense that certain functions appear to be more profoundly influenced and over a longer period of time. In particular the functions which are related to its anaesthetic properties (touch sensitivity and two-point discrimination) tend to be affected earliest, most profoundly and over the longest period of time.

A further point of interest, and one which carries certain theoretical implications, concerns the relation between the sensory and psychological disturbances produced. It is quite clear from the nature of the theory advanced in this paper, namely, that the psychological effects are in part attributable to a kind of sensory deprivation produced directly by the drug, that the sensory changes should precede the psychological. This requirement seems to be adequately fulfilled by our results, as with the exception of the perimetric scores, all sensory tests are showing marked decrement before even the earliest psychological reactions are apparent.

Finally, our investigation shows that the peak of sensory disturbance, excepting in the case of two-point discrimination and touch sensitivity, occurs between approximately 14 and 40 min before the maximal psychological disturbances are produced. This time lag in itself is of interest and suggests that the psychological changes may reflect a gradual process of adjustment to sensory alterations or alternatively, if our theory is incorrect, that the drug directly acts upon higher centres at a later stage.

Further systematic experimental exploration of the effects of phencyclidine are clearly required, both in terms of its disruptive influence on psychological and sensory functions, and upon the relationship between disturbances produced in these functions. Further, it might be argued that on the basis of these results investigations into other psychotomimetic drugs (e.g. lysergic acid diethylamide, psylocybine, etc.) should take account of the part which sensory changes may play in producing some of the psychological effects.

Summary

Previous investigations have suggested that, at least in part, the psychological disturbances which are produced by administration of phencyclidine are attributable to sensory changes. In particular it is

suggested that the symptoms produced by the drug might be a result of a partial sensory deprivation.

The results obtained on 12 experimental and 6 control subjects tend to support this contention, as the drug appears to produce general impairment insensitivity in various modalities. It was also noted that the sensory changes tended to occur well in advance of psychological disturbance, a finding consistent with the theory advanced in this paper.

Acknowledgments. We are grateful to the volunteers who took part in this experiment, and also to Parke Davis and Co., who supplied the drug and supported the investigation. We are also grateful to the Central Research Fund of the University of London for the use of their perimeter.

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Dr. F. S. MORGENSTERN, Institute of Psychiatry,
The Maudsley Hospital, Denmark Hill, London S.E. 5.