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A New Distinction between the Euphoric and the Anti-Depressant Effects of Methylamphetamine

By S. A. CHECKLEY

SUMMARY The psychological effects of an injection of methylamphetamine have been measured in 22 drug-free patients with endogenous depressive illness and in 9 patients with other psychiatric illness. A new distinction between the time course of the euphoric and anti-depressant effects is described. The euphoric effects were seen in the first hour after the injection, but the anti-depressant effects were delayed for 1-3 hours and then lasted for as long as 36 hours. These findings are at variance with the noradrenaline depletion hypothesis of depressive illness which (in its simplest form) predicts an immediate alleviation of depression as a result of an immediate rise in the concentration of noradrenaline at central receptor sites.

Introduction

Measurement of the immediate psychological responses to methylamphetamine may provide a way of studying central catecholaminergic neurotransmission in depressed patients. In animals (C. J. Estler, 1975) and presumably in Man as well (Johnsson *et al*, 1971) the behavioural effects of amphetamines are probably mediated by increases in the concentrations of noradrenaline and dopamine at central receptor sites. Drugs which block the synthesis of these catecholamines inhibit the behavioural effects of amphetamines in a variety of animal species (Weissman *et al*, 1966) including Man (Johnsson *et al*, 1971).

Both the biochemical and the behavioural effects of amphetamines are seen as soon as the drug reaches central receptor sites (Moore, 1977; Johnsson *et al*, 1971). The time course of any anti-depressant effect of amphetamines is unknown. If a functional deficiency of noradrenaline underlies the pathogenesis of some cases of depressive illness then amphetamines should exert an anti-depressant action whose time course is related to that of the changes in concentrations of noradrenaline at central receptor sites. As these concentrations rise the depressions should be alleviated and as they fall the depressions should return.

To follow the time course of any anti-depressant effect of amphetamines it is necessary to consider the other effects of amphetamines. Intravenous injection of an amphetamine frequently causes an initial feeling of drowsiness which is often associated with physical symptoms of autonomic origin (Levine *et al*, 1948; Liddell and Weil-Malherbe, 1953; Simon and Taube, 1946). Many subjects then experience a feeling of alertness, notice they are talking more and describe changes of mood (Lasagna *et al*, 1955; Martin *et al*, 1971; Nathanson, 1937; Smith and Beecher, 1960). Both patients and normal subjects frequently describe an euphoria which is described as a pleasant feeling of well-being and an increased self-confidence. The characteristic symptoms of hypomania are not produced although if they are already present they may be either exacerbated, (Delay, 1949), or relieved (Von Beckmann and Heinemann, 1976). Some normal subjects experience dysphoric symptoms which include both anxiety and sadness (von Felsinger *et al*, 1955). In some cases the whole experience may be dominated either by an abreaction (Jonas, 1954; Liddell and Weil-Malherbe, 1953) or, in some psychotic patients, by the exaggeration of previously held delusional ideas (Myerson, 1936; Pennes, 1954).

In this report the immediate psychological

responses to methylamphetamine and placebo are compared in a group of depressed patients and in a group of patients with other psychiatric illnesses. The prediction is made that an antidepressant response will be seen during the first hour after injection of the drug, at the time when a rise in the concentration of noradrenaline at central receptor sites is most likely.

Methods

The selection of the depressed patients has been described previously (Checkley and Crammer, 1977). Depressed patients met stringent drug-free and diagnostic criteria. The severity and type of the depressive illnesses were recorded using the Hamilton Rating Scale (Hamilton, 1967) and the Carney Roth Garside Questionnaire (Carney *et al*, 1965). Depressed patients with other diagnoses such as personality disorder, alcoholism or dementia were excluded, as were patients with medical illnesses.

A control group was composed of in-patients at the same hospital who met the same drug-free criteria. This group included patients with psychiatric illnesses other than depressive states or functional or organic psychoses.

The rating scales

A series of 16 scales (Norris, 1971) has been found to be suitable for measuring the short-term effects of drugs upon mood in normal subjects (Bond and Lader, 1974). This can be shortened to three visual analogue mood scales, which are labelled alert-drowsy, happy-sad and calm-excited. These were used every 15 minutes up to 60 minutes after injection of methylamphetamine.

A shortened and modified form of the Hamilton Rating Scale for use in depression was administered 2½ hours after the injection of methylamphetamine. The symptoms labelled depressed mood, guilt, suicide, retardation, agitation, psychic anxiety, somatic anxiety, hypochondriasis and insight, were rated according to Hamilton's (1967) definitions but with the modification that symptoms were only rated if they were present during the previous hour. The other items in the Hamilton Rating Scale which cover symptoms such as insomnia, diurnal variation and weight loss were rejected as they cannot be rated in the same way. The full Hamilton Rating Scale for use in depression, and the Carney Roth Garside questionnaire, were administered 1½ hours before administration of the drug.

The experimental procedure

Patients were given a standardized explanation of the research nature of the procedure and of its likely psychological effects. ('You may for a short while feel more happy or more sad, more anxious or more relaxed, or you may notice nothing at all. Any effects you do notice will wear off completely by the end of the test, which can be stopped if you become upset.') Experience confirmed that this was a realistic account of the likely effects, provided that patients with delusional ideas were excluded from study. All patients gave informed consent.

On the day of testing patients were fasted from lunch (12.30 p.m.). Rating scales were administered to depressed patients at 4.00 p.m. A small cannula was inserted into a forearm vein at 5.00 p.m. and five minutes later a placebo injection was given. After a further 30 minutes patients received methylamphetamine (15 mg/75 kgm body weight) by an intravenous injection which was given over 60 seconds.

The analogue scales labelled alert-drowsy, calm-excited and happy-sad were administered at 0, 15, 30, 45, 60, 75 and 90 minutes after injection of the placebo. They were completed independently both by the patient and by the author. The procedure took place in familiar surroundings in the presence of a nurse who already knew the patient. The shortened version of the Hamilton Rating Scale was administered 1½ hours before the injection of methylamphetamine and 2½ hours after the injection.

Results

Twenty-two patients met all the criteria and agreed to participate in the study. Five were unable to complete all of the ratings as they became disturbed after receiving the drug. Two of these patients held paranoid ideas and a third was the only patient in the series who showed an abreaction. Four other patients were too retarded to be able to complete the visual analogue scales every 15 minutes. The

remaining 13 patients formed the depressed group whose immediate mood responses could be studied. Ten were women. The group had a mean age of 50 years and a range from 28 to 75. The mean score on the full Hamilton Rating Scale was 23.6 and the range was from 16 to 35. The diagnostic scores derived from the Carney Roth Garside questionnaire all fell within the endogenous range of 6–13. Three patients met Perris' (1975) criteria for diagnosing bipolar affective illness and 8 patients met his criteria for the diagnosis of unipolar depressive illness. The median number of previous episodes was 9 (range 0–75) and the median duration of the history of treated affective illness was 8 years (range 0–21 years). Eight of the patients with recurrent illness had received a comprehensive range of physical treatments (Shaw, 1977) which had made little or no impact upon the severity of each episode.

The control group included patients with hospital diagnoses of personality disorder (3 cases), obsessive compulsive neurosis (3 cases) and phobic neurosis, Gilles de la Tourette syndrome, and the Klein Levin syndrome (one case each). The control group included 2 women and had a mean age of 26.7 (range 17–34).

The immediate mood responses

The mood responses of the 13 depressed patients and the 9 control patients are shown in Fig 1. Responses along the alert-drowsy dimension are not shown as the mean values remained unchanged throughout the procedure. To obtain a combined measure of the reliability and validity of the measures, individual responses were measured as the maximum recorded change over the first 30 minutes after administration of the drug. The responses as rated by patient and observer were ranked for each group along each dimension. Spearman rank order correlation co-efficients between the ratings made by patients and the observer varied between 0.4 to 0.7. It can be seen from Fig 1 that there is considerable variation in the responses within each group whether these are measured by the patients or by the observer. Indeed so great was this variation that significant drug effects were only detected in a multivariate analysis of variance with repeated measures, if the analysis was arbitrarily restricted to the first 30-minute period after administration of the drug. A detailed examination of the patients' own descriptions of their experiences will explain the source of this variation.

The responses of the psychotic patients will be discussed first as they show the greatest variation. Four of the 13 depressed patients held delusional ideas as rated on the Hamilton Rating Scale. The two patients with delusional ideas of guilt expressed these ideas with increased force throughout the experiment. One asked to be killed and the other wept for 20 minutes while distressed by her ideas of guilt. Both patients rated their mood as happy, saying that they did not deserve to feel sad. Two depressed patients with delusional ideas of bodily change did not become distressed: one described an euphoric reaction and the other showed little response at all. Less variability was noted in the experiences of patients who were not psychotic.

The controls gave straightforward accounts of euphoric experiences—'I feel great, fantastic, calm'. 'I feel like someone who has discovered the Amazon'. 'I feel like shouting 'yipee'. I could go into a party and chat up all the birds'. The non-psychotic depressed patients gave three types of description. Some patients gave qualified descriptions of euphoric experiences—'I feel a little happy . . . I hope I am going to feel happy . . . I don't feel happy any more'. 'I feel happy but I wouldn't if you left the room'. Other depressed patients described feeling more sad and anxious. 'Is it my fault? I feel frightened'. 'I feel frightened but of nothing in particular'. A third group of depressed patients described little change in their mood: two of them were unaware that they had received the drug. No depressed patient described a complete loss of depressive symptoms during the first hour after receiving methylamphetamine.

Delayed effects of methylamphetamine

The delayed effects of methylamphetamine could be studied in all 22 depressed patients. Fig 2 shows scores on the shortened and modified Hamilton Rating Scale made at 4.00 p.m., 1½ hours before the drug was given, and at 8.00 p.m. 2½ hours after the drug was given.

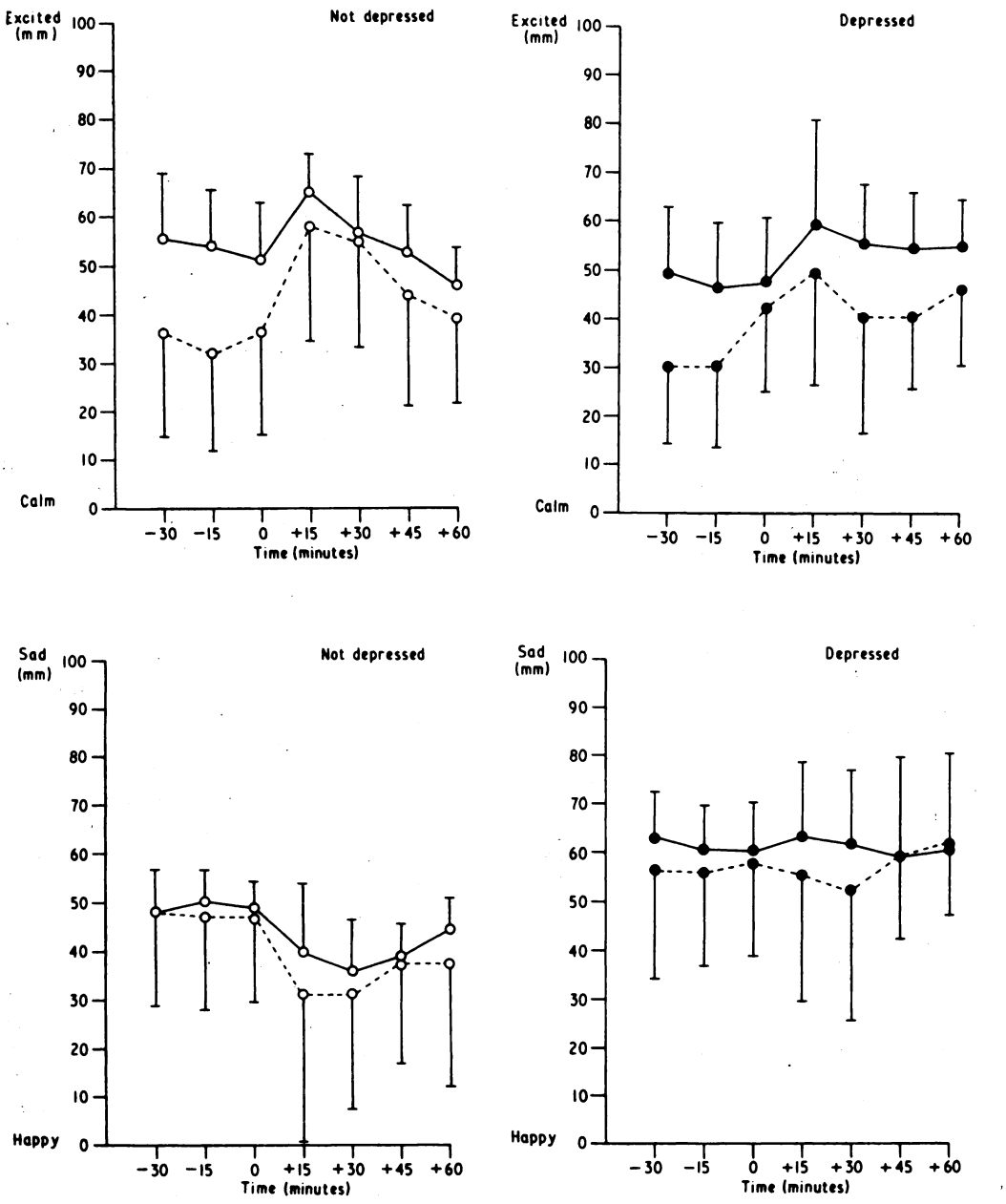

FIG 1.—Mean scores (± SEM) on visual analogue mood scales labelled excited-calm (above) and happy-sad (below) after intravenous injection of placebo at −30 minutes and methylamphetamine (15 mg/75 kgm body weight) at 0 minutes, in patients with endogenous depression ('depressed') and in control patients with other diagnoses ('not depressed'). Self-ratings are shown (0 - - - - -0) and observer ratings (0————0).

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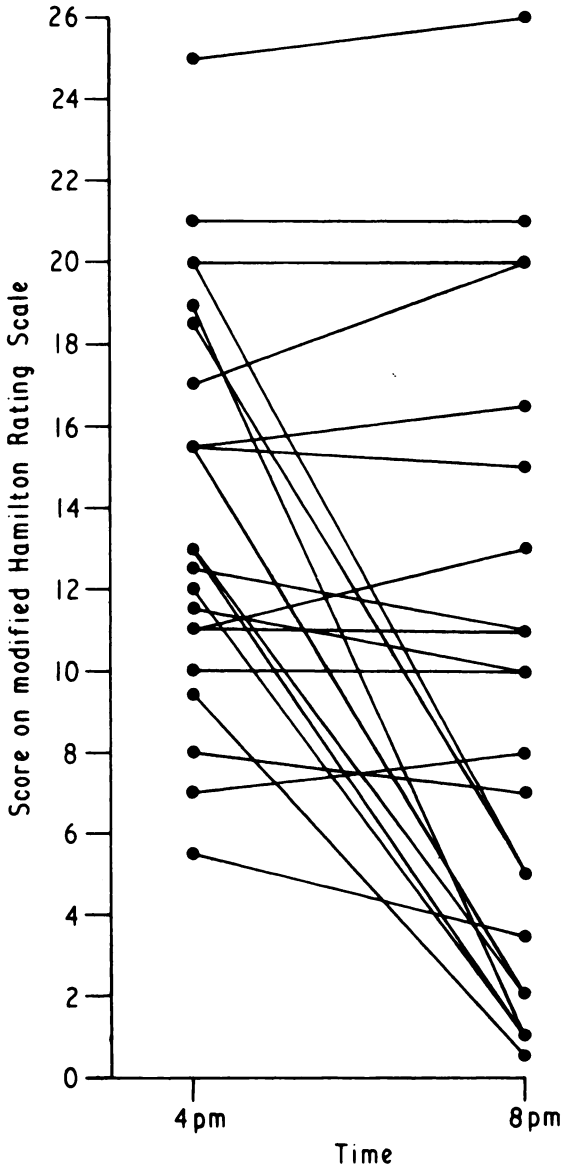

FIG 2.—Scores on a shortened and modified version of the Hamilton Rating Scale for use in depression, rated at 4.00 p.m. and at 8.00 p.m. in depressed patients who received methylamphetamine (15 mg/75 kgm body weight) intravenously at 5.30 p.m.

The responses fell into two groups. In 14 patients the scores changed by three points or less, while in the remaining 8 patients the scores changed by 9 points or more. The significance of this grouping of the responses becomes greater when the residual scores of the 8 patients showing the anti-depressant response are examined. Two patients had scores of 5: both had delusional ideas which persisted after the resolution of all other depressive symptoms. The remaining patients in the group had scores of $2\frac{1}{2}$ points or less, which were always due to symptoms of anxiety. No patient in this group was left with any scores for the items labelled depression, guilt, suicide, retardation, agitation or hypochondriasis and none became euphoric or hypomanic. The anti-depressant responses came on rapidly 1–$2\frac{1}{2}$ hours after receiving the drug. In six patients the depressions returned the next morning either on waking (at the normal time) or shortly thereafter. In one patient, the depression returned 18 hours later and in another it returned 36 hours later.

In three of the patients showing an anti-depressant response to methylamphetamine it has been possible to repeat the procedure under identical drug-free conditions. One patient showed the anti-depressant response on the second occasion but not on the first, while the other two showed it on the first occasion but not on the second.

No differences were found between the patients who showed an anti-depressant response and those who did not when they were compared for age, sex, length of history, total or individual scores on the Carney Roth Garside questionnaire or Hamilton Rating Score, nor when they were classified into having unipolar or bipolar illnesses (Perris, 1975). Control patients did not show any delayed psychological effects of methylamphetamine.

Discussion

The aim of this study was to measure the immediate psychological responses to methylamphetamine in patients with depressive illness. The noradrenaline depletion hypothesis predicts that there will be an immediate alleviation of depression as a result of an immediate rise in the concentration of noradrenaline at central receptor sites. Little immediate alleviation of depression was detected in the patients' descriptions of their mood or in the ratings of mood by patients and observer using visual analogue scales. Yet over the first hour after the injection

of methylamphetamine an immediate release of growth hormone and corticosteroids was measured in these patients (Checkley and Crammer, 1977) and in some patients an immediate dysphoric response was noted. As both the hormonal and the psychological responses are probably mediated by central catecholamines (Estler, 1975; Johnsson *et al*, 1971; Rees *et al*, 1970), it is likely that in these patients the injection of methylamphetamine caused an immediate rise in the concentrations of catecholamines at central receptor sites. The finding that there was no simultaneous alleviation of depression suggests that depression is not due to a simple deficiency of central noradrenaline.

The finding that there was a delayed anti-depressant response also questions the simple noradrenaline depletion hypothesis. However, the same finding suggests that some disturbance in catecholamine function must be related to the pathogenesis of depression. For a massive stimulus to catecholamine systems can reverse depressive symptoms, after a delay of several hours. This delay raises the possibility that post-synaptic events may intervene between changes in concentrations of catecholamines at receptors and subsequent changes in mood.

It is also of interest that the anti-depressant response appears to be complete or nearly complete. The main exception to this is that patients do sometimes retain delusional ideas after the loss of their other depressive symptoms. However, this phenomenon is also seen after ECT, and was, in fact, noted in two of the patients in the present series during earlier depressive episodes. The only other symptom which remained was some anxiety which itself could have been a drug effect. With the exception of these two groups of symptoms the anti-depressant reponses seen in these patients were complete. Such a sudden and striking loss of depressive symptoms is reminiscent of the behavioural switch which has been described in patients with cyclical manic-depressive illnesses (Murphy and Goodwin, 1972; Stoddard *et al*, 1977). A somewhat similar behavioural switch has also been observed after giving L-DOPA (Goodwin *et al*, 1970) which itself stimulates catecholamine function, (Pelton and Chase, 1975).

As this is the first attempt to measure the immediate psychological effects of the parenteral administration of an amphetamine in psychiatric patients, the present report is concerned with methodological issues. The main difficulty is a conceptual one. Although mood scales labelled alert-drowsy, happy-sad and calm-excited are useful for describing normal mood (Bond and Lader, 1974) and for measuring effects of tranquillizers (Bond and Lader, 1973), they have serious limitations when used for measuring effects of amphetamines. The responses described in the present study, like the responses described by Lasagna in normal subjects (Lasagna *et al*, 1955) fall into two categories which may conveniently be labelled as euphoria and dysphoria. These drug-induced mood states are not conveniently measured by analogue scales labelled happy-sad, calm-excited or alert-drowsy. The dysphoric reactions contain variable elements of sadness and anxiety while the euphoric reactions include some alertness and some relaxation as well as a striking euphoria. The alert-drowsy dimension is especially confusing as many patients described feeling both alert and drowsy, either in rapid succession or, paradoxically, at the same time. Severely depressed patients are known to have difficulty rating their own mood and it may be necessary to rely mainly upon ratings made by observers. The present study also demonstrates the unwanted variation that can be introduced by the inclusion of psychotic patients. Abreactions would raise similar issues but were infrequent in the present series, possibly because the dose of methylamphetamine (15 mg/75 Kgm body weight) was small.

These considerations indicate more sophisticated ways of measuring the psychological responses to methylamphetamine. It may be more useful to administer check lists of euphoric and dysphoric symptoms. Preliminary observations suggest that such symptoms can be reliably rated in depressed and recovered patients by independent psychiatrists (Checkley, Cookson and Mikhail, unpublished data).

Finally, it is surprising that the present distinction between the time course of the

euphoric and the anti-depressant response to amphetamines has not been made in earlier studies of the effects of amphetamines upon depressive illness (Gottlieb *et al*, 1950; Kiloh *et al*, 1974; Roberts, 1959; Rudolf, 1956; Van Kammen and Murphy, 1975). It is possible that some of the unusual conditions of the present study highlighted the distinction between the euphoric and the anti-depressant responses. The patients in the present study were selected from many hospitals in order to meet strict criteria, both for the diagnosis of endogenous depression and for exclusion of delayed effects of psychotropic drugs. The experiments were performed later in the day than in the previous studies at a time of spontaneous alleviation of mood, and at a time which approached that of the spontaneous switch mechanism (which is usually seen in the early hours of the morning). Finally, the earlier studies did not closely follow the time course of any drug effects either because the drug was administered orally (van Kammen and Murphy, 1975) or because mood was rated at hourly intervals after administration of the drug (Kiloh *et al*, 1974).

Although the issues raised in this discussion are of general importance, it must be emphasized that the present findings are of a preliminary nature. As no delayed anti-depressant response was anticipated, an appropriately timed placebo control was not included in the experimental design. It seems unlikely, however, that the anti-depressant responses were a placebo effect. They were unexpected by both the patients and the observer, and they occurred in patients who were unresponsive to conventional anti-depressant treatments. Even so, an appropriately time placebo control is required which will also provide control for any diurnal variation in mood. A replication study with these modifications is in progress. For the moment it would be unwise to assume that the anti-depressant and the euphoric effects of methylamphetamine are mediated by the same neurochemical events.

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S. A. Checkley, B.M., M.R.C.P.(U.K.), M.R.C.Psych., *Lecturer in Psychiatry, Institute of Psychiatry, De Crespigny Park, London SE5*

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