AMPHETAMINE AND METHYLPHENIDATE PSYCHOSIS

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AMPHETAMINE and other similar psychomotor stimulants such as methylphenidate (Ritalin), when taken in large amounts, can produce a psychosis, essentially indistinguishable from paranoid schizophrenia. Many subjects who develop amphetamine psychosis on the street are not overtly or latently schizophrenic prior to taking amphetamine; this suggests that the psychosis is a drug produced psychosis. Recently amphetamine has been given experimentally to subjects who were not overtly schizophrenic. It did produce an "amphetamine" psychosis (GRIFFITH *et al.*, 1972).

Since amphetamine psychosis is clinically indistinguishable from an endogenous paranoid psychosis, it may be the best drug-induced model of schizophrenia. Drugs which block stereotyped behaviour produced by amphetamine in animals also have antipsychotic properties in schizophrenic patients. There is a significant amount of indirect evidence linking changes in central dopamine to schizophrenia. *d*-Amphetamine is approximately two times as potent as *l*-amphetamine in producing stereotyped behaviour in rats pretreated with monoamine oxidase inhibitor. In addition *d*-amphetamine is ten times as potent as *l*-amphetamine in producing locomotor stimulation. This evidence would be consistent with the suggestion that stereotyped behaviour is produced by dopamine and locomotor activity by norepinephrine (TAYLOR and SNYDER, 1970). Several authors have shown that cholinomimetic drugs can block stereotyped behaviour produced by the psychomoto stimulants, indicating that stereotyped behaviour may be controlled by a balance of neurotransmitters, such as dopamine vs. acetylcholine (JANOWSKY *et al.*, 1972). If one assumes that in man, *d*-amphetamine is ten times more potent than *l*-amphetamine in producing psychomotor stimulation, and that this is under noradrenergic control and two times as potent in producing amphetamine psychosis than *l*-amphetamine, which is under dopaminergic control, then the isomers may be valuable tools to investigate amphetamine psychosis in man. ANGRIST *et al.* (1971), has produced amphetamine psychosis experimentally in patients who abuse psychomotor stimulants, using both *d* and *l*-amphetamine. *d*-Amphetamine is 1·3 times as potent as *l*-amphetamine in producing the typical amphetamine psychotic picture.

It is important to note that there are two types of psychomotor stimulant produced psychosis. The psychosis produced by large oral doses of amphetamine administered every hour or so for several days is a paranoid psychosis. Recently JANOWSKY *et al.* (1972a, 1973), reported that small dose intravenous administration of methylphenidate 0·5 mg/kg can produce a marked worsening of pre-existing psychosis in patients with active schzophrenic illness. It does not produce psychotic symptoms in normal patients or patients who are in remission. The phenomena of markedly worsening a pre-existing psychosis may be a different one than that producing a

typical paranoid psychosis in the non-schizophrenic subject. A patient's psychosis worsens both qualitatively and quantitatively in the direction of their pre-existing psychosis. Thus, catatonic schizophrenics become more catatomic, without showing paranoid symptoms. Thus, psychosis worsening after the acute intravenous administration produces an exacerbation of the schizophrenic symptoms rather than a uniform paranoid psychosis.

METHOD

A total of 17 actively ill schizophrenic patients, who were in good health without cardiovascular or other physical illness were administered active drug by a single injection, preceded and followed by placebo injections every 5 min. Equimolar doses of *d*-amphetamine sulphate solution, *l*-amphetamine succinate solution, or methylphenidate hydrochloride solution in random order on different days was administered. A blind rater noted each patient for changes in a number of variables every 10 min using a 5 point rating scale. The items rated included: Psychosis, conceptual disorganization, unusual thoughts, anger, irritable interaction, talkativeness, as well as "activation" and "inhibition" as defined previously (JANOWSKY *et al.*, 1972).

In each experiment, the rater and patient were blind to when in an IV injection sequence active drug was substituted for placebo and which active drug was given. Blood pressures and pulses were monitored every 5 min. Data was analysed by comparing average scores and change scores between the baseline–placebo phases and the 10–20, 20–30 and 30–40 min periods after active drug injection for each of the experimental drugs. Thus, each patient served as his own control. Patients received *d* and *l*-amphetamine, 20 mg (0·11 mM.) and 28 (0·11 mM) respectively, methylphenidate 29 mg (0·11 mM) and *d*-amphetamine 10 mg (0·55 mM) and *d*-amphetamine 4 mg (0·022 mM).

For ethical reasons, it was sometimes not possible to give every subject all the injections in the series. All comparisons between drugs were made in subjects who received both injections.

In addition, in order to evaluate the ability of acetylcholine to antagonise psychostimulant effects, a total of 24 schizophrenic patients received a series of placebo injections every 5 min followed by injection of 0·5 mg/kg methylphenidate over a 30 sec. period of time. In nine patients two placebo injections at 5 min intervals were followed by a series of either: (1) every 5 min placebo injections, or (2) 0·5 mg physostigmine injections every 5 min until methylphenidate antagonism occurred or 2·5 mg had been given, or (3) neostigmine 0·25 mg injection given every 5 min until 1·25 mg had been given. After the above series had been given, placeboes were injected every 5 min for 30 min.

Also, the ability of methylphenidate to reverse the physostigmine induced "inhibitory state" was evaluated using the same design as above except that the physostigmine or neostigmine was given first, followed by methylphenidate.

RESULTS

In actively schizophrenic patients, methylphenidate produced a marked worsening of the schizophrenic symptoms causing a doubling of the psychosis scores (JANOWSKY *et al.*, 1972 and Table 1). *d*-Amphetamine worsened psychotic symptoms somewhat, but was less potent than methylphenidate. *l*-Amphetamine was the least potent of the 3 drugs. *d*-Amphetamine 10 mg and *d*-amphetamine 4 mg were less potent than *l*-amphetamine 28 mg. The results from each of several experiments were combined

TABLE 1. CHANGE SCORES REPRESENTING DIFFERENCES BETWEEN THE AVERAGE BASELINE-PLACEBO PHASE RATINGS AND THE AVERAGE OF RATINGS DONE AT 10 AND 20 MIN AFTER INTRAVENOUS PSYCHOSTIMULANT ADMINISTRATION

	Methylphenidate† 29 mg ($N = 10$)	*d*-amp. 20 mg ($N = 18$)	*l*-amp. 28 mg ($N = 14$)	*d*-amp. 10 mg ($N = 6$)	*d*-amp. 4 mg ($N = 8$)
Psychosis (global)	0·48 ± 0·16**	0·36 ± 0·15*	0·22 ± 0·11*	0·20 ± 0·09*	0·14 ± 0·08*
Conceptual disorganisation	0·88 ± 0·27**	0·53 ± 0·17**	0·22 ± 0·16	0·0	0·04 ± 0·09
Unusual thoughts	0·72 ± 0·23**	0·52 ± 0·18**	0·25 ± 0·11*	0·08 ± 0·09	0·06 ± 0·08
Combined psychosis score	2·08 ± 0·60**	1·42 ± 0·44**	0·69 ± 0·32*	0·28 ± 0·14*	0·24 ± 0·17
Anger	0·56 ± 0·35	0·09 ± 0·22	0·35 ± 0·19*	0·0	0·26 ± 0·20
Irritable	0·26 ± 0·26	−0·08 ± 0·12	0·23 ± 0·18	0·22 ± 0·22	0·14 ± 0·17
Activation (interaction and talkativeness)	1·80 ± 0·26***	1·22 ± 24***	0·56 ± 0·21*	0·45 ± 0·14*	0·63 ± 0·27*

* = $P < 0·05$, ** = $P < 0·01$, *** = $P < 0·001$ = Statistical significance of change scores.
† = *d*-amphetamine (20 mg), *l*-amphetamine (28 mg), and methylphenidate (29 mg) are equimolar.

to arrive at drug potencies relative to the psychosis worsening effects of *l*-amphetamine. Methylphenidate was also more potent in activating the patients by increasing their talkativeness and interactions. *d*-Amphetamine was less potent than methylphenidate but more potent than *l*-amphetamine. *d*-Amphetamine-4 mg and 10 mg were of comparable potency to *l*-amphetamine 28 mg.

The experiment concerning dopaminergic-cholinergic balance can be done in one of two ways. One may produce an increase in psychosis and activation by methylphenidate and block this by the administration of physostigmine, or produce an inhibitory state by physostigmine and then reverse this by methylphenidate.

In the experiment in which methylphenidate was given followed by physostigmine, methylphenidate produced a 50 per cent increase in psychosis ratings. When physostigmine was administered after methylphenidate there was essentially no net increase in psychosis, so that physostigmine effectively reversed the psychosis worsening property of methylphenidate (Table 2). Methylphenidate also increased interactions, and this effect was blocked by physostigmine. When a psychomotor retardation syndrome was produced by physostigmine, this can be reversed by methylphenidate. Physostigmine failed to alter the baseline psychosis when given alone.

DISCUSSION

All of the psychomotor stimulants can markedly worsen psychosis and can also increase activation as manifested by talkativeness and increased interactions. In order of potency, methylphenidate is more potent than *d*-amphetamine, which itself is more potent than *l*-amphetamine. Lower doses of *d*-amphetamine (10 mg, 4 mg) are essentially of equal potency to *l*-amphetamine-28 mg in producing activation. If one focuses on the relationship of *d* and *l*-amphetamine, *d*-amphetamine is slightly more potent than *l*-amphetamine in activating psychosis and increasing activation. Furthermore, the degree of its greater potency in these two behaviours is approximately equal. Thus, a different relationship between the differential potency of

TABLE 2A. EFFECTS OF METHYLPHENIDATE IN ANTAGONISING PHYSOSTIGMINE INDUCED STATE ($N = 7$)

	Baseline	P	Physostigimine	P	Physostigmine Methylphenidate
Inhibition	7·7 ± 2·8	0·02	13·9 ± 3·5	0·02	8·9 ± 2·0
Activation	4·9 ± 1·1	0·07	2·9 ± 0·9	NS	3·8 ± 0·6
Psychoses	1·4 ± 0·6	NS	1·5 ± 0·5	NS	2·0 ± 0·3

B. EFFECTS OF PHYSOSTIGMINE IN ANTAGONISING METHYLPHENIDATE INDUCED PSYCHOSIS ACTIVATION AND INCREASED INTERACTIONS IN SCHIZOPHRENICS

Methylphenidate + placebo	Baseline score	P	15 min. post methylphenidate score	P	45 min post methylphenidate score
Psychosis	1·96 ± 0·24	<0·0002	3·00 ± 0·27	<NS	2·89 ± 0·27
Interaction	1·67 ± 0·17	<0·0003	2·76 ± 0·20	<0·03	2·54 ± 0·20
Methylphenidate + physostigmine**					Physostigmine
Psychosis	1·89 ± 0·46	<0·003	2·93 ± 0·53	<0·004	1·96 ± 0·48
Interaction	1·96 ± 0·34	<0·002	3·04 ± 0·24	<0·006	1·81 ± 0·37

*$N = 24$, **$N = 9$

P values represent the comparison between two adjacent columns.

the two isomers of amphetamine on these two behaviours exist in man than in the rat, if one assumes that psychoses corresponds to stereotyped behaviour and activation corresponds to locomotor activity. In man, both behaviours occur with a potency ratio consistent with a dopaminergic theory of schizophrenia. Space does not permit a detailed review here, and reference is made to our previous exposition (JANOWSKY *et al.*, 1972).

If brain monoamine oxidase is decreased in schizophrenic brain, it is tempting to speculate that the methylphenidate-induced psychosis activation is related to the monoamine oxidase deficit, particularly in that central catecholamines released by methylphenidate could be expected to be released in active form, since they would not be effectively metabolized intraneuronally (MURPHY and WYATT, 1972). It is relevant to note that methylphenidate releases preferentially from the monoamine stores, a finding which would be consistent with the greater potency of methylphenidate, relative to amphetamine in worsening psychosis (SCHEEL-KRUGER, 1971).

There is a substantial body of evidence indicating that stereotyped behaviour is controlled by a balance between the dopaminergic and the cholinergic system. It is relevant to examine whether increasing brain acetylcholine with physostigmine can block the psychosis-activating properties of methylphenidate. When physostigmine was administered prior to methylphenidate, it prevented the psychosis worsening. This indicates that the worsening of the psychosis produced by methylphenidate and presumably mediated by dopamine is controlled by a dopaminergic-cholinergic balance, as is stereotyped behavior. Is the underlying psychosis also controlled by an endogenous dopaminergic factor which is balanced by a cholinergic system? The observation that physostigmine does not reduce psychosis would suggest that the underlying psychotic process is not as easily amenable to the effects of altering cholinergic tone as is the worsening of the psychosis produced by methylphenidate. It is relevant to note that antipsychotic drugs do not always immediately block

psychosis, the therapeutic improvement occurring over weeks rather than hours in many instances.

The activating effects of methylphenidate are blocked by physostigmine, and the inhibition syndrome produced by physostigmine is blocked by methylphenidate: indicating the activation is under control of adrenergic-cholinergic balance.

It is appropriate to record the obvious caution in interpreting experiments such as this due to the inexactitude of clinical studies, the speculative nature of the dopaminergic theory of schizophrenia, as well as the reliance in this theorizing on the assumption that data derived from rats by Snyder is generalisable to (1) a greater variety of situations involving the relationship between *d* and *l*-amphetamine, stereotyped behavior, dopamine and norepinephrine release and uptake and (2) to man.

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