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Methylphenidate and Serum Prolactin in Man

David S. Janowsky, Pierre Leichner, Donal Parker, Lewis Judd, Leighton Huey, and Paul Clopton

The Departments of Psychiatry and Medicine, University of California at San Diego, Medical School, La Jolla, California 92103, U.S.A.

Abstract. Methylphenidate induces psychostimulation and increases cardiovascular parameters, and its psychostimulant effects have been proposed to occur via a dopaminergic mechanism. The effect of methylphenidate on serum prolactin was utilized as a method of evaluating methylphenidate's central dopaminergic effects. Methylphenidate was not found to exhibit a consistent effect on serum prolactin. Thus, its effect on serum prolactin does not parallel its behavioral activating properties, suggesting that such activation may not involve dopamine. Possibly, norepinephrine or other noncatecholaminergic neurotransmitters are involved in methylphenidate-induced behavioral activation.

Key words: Methylphenidate – Prolactin – Behavioral activation – Dopamine – Psychostimulation

Intravenous psychostimulants, including methylphenidate, reportedly increase hallucinations, delusions, pathologic responses to projective tests, uncommon word associations, and talkativeness in actively ill schizophrenic patients, and talkativeness in normal subjects, nonpsychotic psychiatric patients, and remitted schizophrenics (Janowsky et al., 1973, 1976, 1977). These effects are most prominent 15–30 min after methylphenidate administration, and last between 1 and 2 h. They have the same time course as increases in pulse rate and blood pressure, and do not occur when placebo is given (Janowsky et al., 1973, 1977).

Although the biochemical mechanism by which these effects occur is not proven, data from animal experiments (Scheel-Krüger, 1971; Ferris et al., 1972; Harris and Baldessarini, 1973; Thornberg and Moore, 1973) suggest that catecholamines are involved. Methylphenidate increases stereotyped gnawing behavior in rats, probably a dopamine-mediated phenomenon, and dopamine and norepinephrine are released by methylphenidate from the presynaptic, intraneuronal, bound catecholamine stores (Scheel-Krüger, 1971). Furthermore, dopamine is selectively released from rat striatum by methylphenidate (Ferris et al., 1972). On the basis of these observations, dopamine has been proposed to cause psychostimulant-induced behavioral activation (Janowsky et al., 1973), but no human studies have actually demonstrated that psychostimulants exert a central dopaminergic effect.

One way to study a drug's effect on central dopamine is to study the effect of the drug on serum prolactin levels (Meltzer et al., 1974; Meltzer and Fang, 1976; Sachar et al., 1975; Lal et al., 1973). There is evidence that alterations in central dopamine activity influence serum prolactin. Serum prolactin levels increase when central dopaminergic activity diminishes, probably through inhibition of prolactin-release-inhibiting factor (Frantz, 1973). Thus, all antipsychotic agents, including reserpine and all other classes of antipsychotic drugs, increase serum prolactin levels (Sachar et al., 1975; Wilson and Hamilton, 1975; Clemens et al., 1975; Rubin, 1976). In contrast, L-dopa and apomorphine (Lal et al., 1973; Martin et al., 1974; Smalstig et al., 1974), both agents that increase central dopaminergic activity, significantly decrease serum prolactin levels. It is, however, important to note that prolactin levels also are influenced by such other factors as exercise, stress, orgasm, thyroid-releasing factor, pregnancy, hypoglycemia, and estrogen (Frantz and Suh, 1974).

This study explored the biochemical basis of methylphenidate's behavioral activating effects in man by studying its effect on prolactin levels and the relationship of this effect to changes in behavioral activation. Since methylphenidate presumably increases central dopaminergic activity, we predicted that serum prolactin levels would fall following methylphenidate infusion, and that this fall would parallel methylphenidate-induced changes in behavioral activation and cardiovascular parameters.

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Table 1. Prolactin responses of 24 psychiatric patients given 0.5 mg/kg i.v. methylphenidate

Patient/ sex/age	Diagnosis[a]	Psychotropic drugs (mg/day p.o.)	Serum prolactin (ng/ml)			
			-30^m	-1^m	$+30^m$	$+60^m$
1/M/24	Schiz paranoid	None	9.8	7.7	8.6	4.3
2/M/27	Schiz paranoid	None	–	4.0	2.0	2.8
3/M/25	Schiz paranoid	None	–	4.3	2.9	2.2
4/F/19	Acute Schiz Epi	Flurazepam 30 mg	–	7.0	3.4	2.6
5/F/23	Schiz Chr Und	None	–	3.9	3.5	6.1
6/M/24	Schiz affec type, Dep	None	5.3	6.8	4.5	5.8
7/M/19	Dep neurosis	None	–	5.8	3.6	6.3
8/M/24	Dep neurosis	None	–	5.8	3.0	6.8
9/F/28	Dep neurosis	None	–	7.8	5.5	5.7
10/M/61	M-D, Dep	None	–	2.7	6.5	16.0
11/M/27	M-D, Dep	None	8.7	8.1	4.5	5.4
12/M/19	M-D, Dep	Benztropine 2 mg	–	4.5	4.0	3.8
13/M/44	Alcoholism	None	5.7	7.2	5.5	5.2
14/M/54	Alcoholism	None	–	3.8	5.8	5.3
15/M/44	Alcoholism	None	8.3	7.8	5.5	4.3
16/M/37	Alcoholism	None	–	6.4	4.3	2.8
17/M/31	Alcoholism	Lithium 500 mg	–	4.4	3.2	4.3
18/M/47	Alcoholism	Lithium 800 mg	0.8	5.0	4.3	6.2
19/M/37	Alcoholism	None	–	2.9	3.1	2.5
20/M/38	Alcoholism	None	5.4	6.2	9.0	6.2
21/M/32	Alcoholism	None	–	7.4	7.3	3.8
22/M/34	Drug depend	None	–	6.5	7.1	6.2
23/M/36	Drug depend	Phenobarbitol 200 mg	–	9.7	5.1	6.0
24/M/41	Drug depend	None	–	7.7	14.7	9.8
Mean ± SEM				6.0 ± 0.4	5.3 ± 0.6	5.4 ± 0.6[b]

[a] Schizophrenia, paranoid type – schiz paranoid; schizophrenia, schizo-affective type, depressed – schiz affec type, Dep; acute schizophrenic episode – acute schiz Epi; schizophrenia, chronic undifferentiated type – schiz Chr Und; depressive neurosis – Dep neurosis; manic depressive, depressed type – M-D, Dep; drug dependency – drug depend

[b] Data presented as mean ± standard error of mean of all 24 patients

Materials and Methods

Subjects. Subjects were twenty-four psychiatric inpatients. The sex, age, primary diagnosis, and dosage of prescribed medications of each of the subjects is outlined in Table 1. None of the patients had been receiving antipsychotic medications (neuroleptics) while participating in the study. Three of the patients were females and 21 were males.

The ages of the patients ranged from 19 – 61 years (mean age = 33.1 years). All patients were diagnosed at discharge according to the classifications of the American Psychiatric Association Diagnostic and Statistical Manual (DSM-II, 1968), based on the consensus of the patient's psychiatric resident, inpatient psychiatric ward chief, and one of us (DSJ). Six of the patients were diagnosed as schizophrenics (1 chronic undifferentiated; 3 paranoid; 1 schizo-affective depressed; 1 acute schizophrenic episode); 3 were diagnosed as manic depressive, depressed; 3 were diagnosed as having a depressive neurosis; 3 were diagnosed as drug-dependent; and 9 were alcoholics (habitual excessive drinking) who had completed alcohol withdrawal. None of the schizophrenics were chronically institutionalized psychiatric inpatients, although most had experienced one or more previous psychotic episodes. Most were able to function marginally between psychotic episodes. The nonschizophrenic patients in the study, like the schizophrenics, were treated with short-term hospitalization and were acute, rather than chronic, psychiatric patients.

All patients were in good physical health, without evidence of cardiovascular disease, organic brain dysfunction, or other physical illness. All had been voluntarily admitted to an inpatient psychiatric unit for treatment, and fully informed consent was obtained from each.

Procedure. Each patient received a single dose of 0.5 mg/kg methylphenidate given over a 30-s time period through a slowly running i.v. unit. Patients remained seated throughout the experiment. Blood pressure, pulse, talkativeness, and anxiety were monitored every 10 min beginning immediately before and ending 1 h after methylphenidate infusion, as described previously (Janowsky et al., 1973, 1976, 1977).

Blood samples were withdrawn through the i.v. unit just before and at 30 and at 60 min after methylphenidate infusion. In certain patients, blood samples were also drawn 30 min before infusion. Blood samples were centrifuged and the plasma frozen and stored for prolactin radioimmunoassay. The assay for prolactin employed rabbit anti-hPRL at final dilution of 1 : 130000, a standard and I^{125} label of U. J. Lewis' hPRL (203-1) with a potency of 30 IU/mg of Lowry protein, and was capable of 1 – 2 ng/ml sensitivity (Parker et al., 1973). Duplicate prolactin assays of 19 samples attained a reliability coefficient of 0.956.

In addition to receiving methylphenidate, 6 subjects received a second trial in which saline was infused to provide a placebo control.

Analysis. Serum prolactin levels were available for 24 of the patients. Talkativeness and anxiety ratings and cardiovascular data were obtained for 17 of the patients. To evaluate the influence of diagnostic classification (diagnoses of schizophrenia vs. all other patient diag-

Table 2
Effects of active and placebo methylphenidate (0.5 mg/kg i.v.) on serum prolactin in 5 psychiatric inpatients

Diagnosis[a]	Serum prolactin level (ng/ml)					
	Placebo			Active		
	Baseline	+30m	+60m	Baseline	+30m	+60m
Drug depend	7.7	9.8	5.3	9.7	5.1	6.0
M-D Dep	9.7	10.0	10.0	8.1	4.5	5.4
Schiz paranoid	5.5	4.7	5.1	7.7	8.6	4.3
Schiz affec type Dep	5.1	6.5	4.9	6.8	4.5	5.8
M-D Dep	6.5	9.2	5.0	4.5	4.0	3.8
Mean ± SEM	6.9 ± 0.8	8.0 ± 1.0	6.1 ± 1.0	7.4 ± 0.9	5.3 ± 0.8	5.1 ± 0.4

[a] M-D Dep – manic depressive illness, circular type, depressed; Drug depend – drug dependence; Schiz paranoid – schizophrenia, paranoid type; Schiz affec type Dep – schizophrenia, schizo-affective type, depressed

noses) on prolactin levels and on cardiovascular and behavioral parameters, these variables (between-subjects factors) were tested using analysis of variance techniques.

In the placebo-control study, complete cardiovascular and behavioral data were obtained for all 6 patients. Control prolactin levels were obtained for 5 patients. Analyses of variance (two within-subjects factors) were used to compare the differential effects of methylphenidate and saline-placebo.

Results

As shown in Table 1, a total of 24 patients received methylphenidate infusions. Infusion was followed by a small, insignificant average decrease in serum prolactin levels ($F = 0.68$, $df = 2/46$). Changes in prolactin levels following methylphenidate infusion did not differ between schizophrenics and those with other diagnoses ($F = 0.78$, $df = 2/44$). The average prolactin level was, however, slightly lower for schizophrenics (4.58 ± 0.47) than for those with other diagnoses (5.79 ± 0.35), although this difference was not significant ($F = 2.14$, $df = 1/22$, $P = 0.15$).

As shown in Table 2, five of the patients participated in the placebo-control study, receiving an additional trial in which saline was infused instead of methylphenidate and in which serum prolactin levels were drawn. Prolactin levels decreased slightly following methylphenidate infusion and increased slightly following saline infusion. This difference, however, did not attain statistical significance ($F = 2.75$, $df = 2/8$, $P = 0.15$).

Cardiovascular Response. For the 17 patients from whom cardiovascular data was obtained, average systolic and diastolic blood pressure and pulse rate also increased significantly following methylphenidate infusion ($F = 5.05$, 7.73, 18.06 respectively, $df = 6/96$, $P < 0.001$). Diagnosis did not exert a significant effect on the cardiovascular parameters. Increases in pulse and blood pressure usually peaked by 30 min and decreased thereafter.

For the 6 patients utilized in the placebo-control study, increases in pulse rate following methylphenidate infusion were significantly greater than those following placebo ($F = 4.55$, $df = 6/30$, $P < 0.005$). Changes in systolic and diastolic blood pressure did not significantly differ from placebo ($F = 1.25$ and 1.74, respectively, $df = 6/30$).

Talkativeness and Anxiety Ratings. For the 17 patients so rated, talkativeness ratings increased significantly following methylphenidate infusion ($F = 16.44$, $df = 6/96$, $P > 0.001$). Talkativeness ratings generally increased for 20 min and decreased thereafter.

For the 6 patients utilized in the placebo-control study, talkativeness ratings did not increase significantly more following methylphenidate than they did following saline-placebo.

Average anxiety ratings of the 17 patients so rated also did not change significantly following methylphenidate infusion ($F = 1.07$, $df = 6/96$), and response to methylphenidate administration did not differ significantly from the response to saline in the placebo-control study ($F = 0.24$, $df = 6/30$). The effects of methylphenidate on talkativeness, pulse rate, and systolic and diastolic blood pressure are outlined in Table 3.

Discussion

The data indicate that prolactin levels which are normal at baseline are not significantly changed by methylphenidate. These results are analogous to those reported by Van Kammen et al. (1977), in which amphetamine had no consistent effect on schizophrenic subjects receiving and not receiving Pimozide. They differ from the results of Lu and Meites (1971), showing that *d*-amphetamine increases serum prolactin in rodents.

Certain methodologic weaknesses exist in our study which deserve comment. First, our placebo-control

Table 3
Effects of i.v. methylphenidate (0.5 mg/kg) on talkativeness, pulse rate, and systolic and diastolic blood pressure in 17 psychiatric in patients

[a] All results expressed in mean ± SEM

Time (min)	Talkativeness (0–5 points)	Pulse (rate/min)	Blood pressure[a]	
			Systolic	Diastolic
Baseline	1.94 ± 0.23	85.06 ± 4.21	123.41 ± 3.59	80.82 ± 1.94
10	3.00 ± 0.27	118.94 ± 6.15	134.65 ± 3.45	88.53 ± 2.47
20	3.29 ± 0.25	115.53 ± 5.34	137.18 ± 3.59	91.18 ± 2.56
30	3.18 ± 0.18	110.82 ± 5.76	136.59 ± 3.38	89.12 ± 2.39
40	2.94 ± 0.25	107.24 ± 4.96	134.88 ± 3.50	89.88 ± 2.18
50	2.88 ± 0.23	107.06 ± 5.28	133.88 ± 3.40	90.12 ± 2.27
60	2.65 ± 0.24	103.18 ± 4.91	132.24 ± 3.10	89.77 ± 2.52

study did not contain a sufficient number of subjects to determine definitively whether or not methylphenidate actually lowers serum prolactin relative to placebo. Furthermore, it would have been advisable to obtain more baseline prolactin samples in our subject group.

Nevertheless, our results suggest that nonelevated prolactin levels, if at all, are only minimally and nonsignificantly decreased by methylphenidate. However, the results of the placebo-control study, although inconclusive, do suggest that methylphenidate may cause a very slight relative decrease in normal serum prolactin levels. Nevertheless, the effect of methylphenidate on normal prolactin levels is certainly much weaker and less dramatic than that caused by the dopamine precursor L-dopa and the dopamine agonist apomorphine (Lal et al., 1973; Sachar et al., 1973, 1976; Smalstig et al., 1974).

The observed effect of methylphenidate on prolactin levels is difficult to explain, given methylphenidate's presumed dopaminergic effects (Ferris et al., 1972; Scheel-Krüger, 1971). Methylphenidate might exert antagonistic pharmacologic effects that both increase and decrease prolactin levels, leading to a net lack of change in normal levels. Alternatively, perhaps methylphenidate does not effect the prolactin-regulating system, as does L-dopa and apomorphine. Possibly, the infusion of methylphenidate caused stress that led to a rise in serum prolactin. It is, however, important to note that our subjects showed no change, rather than an increase, in anxiety following methylphenidate infusion. Finally, it is possible that our method was not sensitive enough to detect small decreases in initially low prolactin levels, although the high degree of correlation of our duplicate samples suggests otherwise.

The lack of effects of methylphenidate on serum prolactin may help clarify the nature of the central neurotransmitter changes underlying psychostimulant-induced behavioral activation. Our results do not support the hypothesis that methylphenidate-induced behavioral activation is mediated by dopamine (Janowsky, et al., 1973). If increases in dopamine mediate psychostimulant-induced behavioral activation, we would have expected a decrease of serum prolactin in our patients. In our study, however, serum prolactin levels were minimally or not at all affected by methylphenidate, yet methylphenidate caused profound behavioral activation in these patients. Furthermore, relatively low doses of oral L-dopa (500 mg) and s.c. apomorphine (0.75–1.5 mg) consistently and vigorously reduce prolactin levels (Lal et al., 1973; Martin et al., 1974; Smalstig et al., 1974; Franz and Suh, 1974; Sachar et al., 1973), but these agents, given in the above doses, generally cause no behavioral activating effects or sedation (Angrist, personal communication, 1975). Also, lithium carbonate, which partially blocks methylphenidate-induced behavioral activation, does not effect serum prolactin levels (Huey et al., 1977).

Thus, our study does not offer evidence that the presumed central dopaminergic effects of methylphenidate underlie methylphenidate-induced increases in talkativeness and the activation of psychotic symptoms. Possibly, methylphenidate's psychostimulant effects and effects on serum prolactin are dissociated. Since methylphenidate is known to exert multiple central effects, it is possible that methylphenidate-induced behavioral activation may be mediated by such other neurotransmitters as norepinenephrine, gamma amino butyric acid, or acetylcholine, rather than by dopamine.

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