METABOLIC AND BODY WEIGHT CHANGES FOLLOWING THE REDUCTION OF MAINTENANCE NEUROLEPTICS
—A PILOT STUDY—

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ABSTRACT:

A total of eight blood samples were taken at weekly intervals from each of five chronic schizophrenics, four of whom were obese. Body weight was measured simultaneously. On the day before the fifth sampling, the maintenance dose of neuroleptic medication was reduced by half in each case. Following the reduction in dosage, significant decreases in body weight and increases in free fatty acids were observed, although no changes in other lipid fractions were found. This result is consistent with the hypothesis that neuroleptic-induced obesity is due to altered peripheral lipid storage as well as to overeating.

KEY WORDS : Shizophrenia, Obesity, Lipid

INTRODUCTION

The aetiology of obesity, which appears among psychiatric patients on neuroleptic medication, has been considered by the author (*Kitamura* (1976)) as follows. The release of free fatty acids (FFA) from adipose tissue is enchanced by hormone sensitive lipase which does not, however, affect the uptake of lipids from the blood stream into adipose tissue. The activity of hormone sensitive lipase may be blocked by neuroleptics through the suppression of a variety of hormones which may otherwise stimulate hormone sensitive lipase. Eventually, in the patients medicated with neuroleptics, triglyceride (TG) will be stored excessively in adipose tissue, causing overweight. Therefore if neuroleptics are discontinued or reduced, excessively stored TG will be hydrolised into FFA and released into the blood stream.

The present investigation, therefore, is concerned with the metabolic effects of the reduction of long term neuroleptic treatment on the chronic schizoprenics. Specifically it was hypothesised that body weight would be decreased whereas FFA would be increased.

PATIENTS AND METHODS

To avoid interference from variables related to menstruation, five male chronic schizophrenic in-patients were chosen for the study. Each patient had been hospitalised for at least five years, was without active symptoms and had been stabilized on neuroleptic medication for at least the previous year. Participation was voluntary and the expeimental procedures were fully explained to the subjects.

The profiles of the sample patients are shown in the table 1. The mean age ($\pm$SEM) was 45 ± 5 years old, the mean duration of hospitalisation ($\pm$SEM) was 18 years 10 months±7 years 3 months.

Table 1 Patients' profile

Patient	Age	Hospitalisation	Height	Weight	Excess	Weight
No.	(years)	(years, months)	(cm.)	(kg.)	(%)	
1	52	18. 00	168	66. 5	7. 4	
2	49	24. 10	150	65. 0	26. 2	
3	40	18. 10	162	75. 0	29. 5	
4	50	7. 03	165	84. 5	41. 3	
5	48	25. 01	164	65. 5	10. 8	
Mean	48	18. 10	161. 8	71. 3	23. 0	
SEM	5	7. 03	6. 9	8. 4	14. 0	

Table 2 Medication——daily dosage

Patient	Name of drugs	Before the reduction	After the reduction
No.		of drug	of drug
1	Levomepromazine	100 mg	50 mg
	Methylperidol	30 mg	15 mg
	Promethazine	100 mg	50 mg
	Mg. ust.	1. 0	1. 0
2	Pipamperone	150 mg	75 mg
	Chlordiazepoxide	30 mg	30 mg
	Ethopropazine	60 mg	60 mg
	Nitrazepam	5 mg	5 mg
	Levomepromazine	10 mg	5 mg
3	Spiperone	6 mg	3 mg
	Promethazine	100 mg	50 mg
	Trihexyphenidyl	10 mg	10 mg
4	Perazine	150 mg	75 mg
	Perphenazine	12 mg	6 mg
	Mg. ust.	1. 0	1. 0
5	Pipamperone	300 mg	150 mg
	Chlorpromazine	300 mg	150 mg
	Perphenazine	15 mg	8 mg
	Promethazine	100 mg	50 mg
	Mg. ust.	1. 0	1. 5

The expected weight for each individual of a particular height was derived from *Matsuki's* table of the standard weight of Japanese adults (*Matsuki et al.* (1971)). According to *Matsuki et al.* who defined obesity as more than 10% above the expected weight, four out of the five subjects were obese. Each subject's medication is shown in table 2.

Blood samples were taken weekly, before breakfast on a total of eight occasions. At the same time body weight was measured. The medications were reduced to approximately half dosage, on the day before the 5th sampling day. Therefore the first four samples were taken before the drug reduction and the latter four following the drug reduction. Total lipid, phospholipid, TG, FFA, cholesterol, cholesterol ester, and lipoprotein fractions (α, pre β, β, chylomicron) were measured. Cholesterol/cholesterol ester ratio and β lipoprotein/α lipoprotein ratio were calculated. Lipoprotein fractions of the 1st week, total blood of the 4th week, and the body weight of the 5th week were not done because of

technical problems.

The drugs used were neuroleptics which included phenothiazines, butyrophenones, anxiolytics, antiparkinson drugs, hypnotics, and others (table 2). Only neuroleptics were reduced to half dosage whereas the prescription of other kinds of drugs were not changed. No p.r.n. (*pro re nata*) medications were prescribed to any patient during the survey period.

The Sign Test was used for the statistical treatment (*Siegel* (1956)).

RESULTS

Table 3 shows the data concerning body weight, lipid components, and lipoprotein fractions. No

Table 3　Body weight and blood levels of lipid fractions and lipoprotein
fractions before an after the drug reduction (mean ± SEM)

Item	Unit	Before the drug reduction	After the drug reduction	One-tailed Sign Test
Body weight	kg	70. 9 ± 7. 8 (20)	69. 1 ± 7. 8 (15)	P = 0. 031
Total lipid	mg/dl	559. 1 ± 49. 4 (15)	556. 2 ± 53. 4 (20)	N. S.
Phospholipid	mg/dl	167. 7 ± 24. 7 (15)	182. 2 ± 22. 1 (20)	N. S.
Triglyceride	mg/dl	198. 2 ± 31. 3 (15)	181. 1 ± 29. 4 (20)	N. S.
Free fatty acids	mg/dl	6. 50 ± 2. 61 (15)	9. 78 ± 3. 71 (20)	P = 0. 031
Cholesterol	mg/dl	186. 5 ± 16. 0 (15)	183. 2 ± 19. 3 (20)	N. S.
Cholesterol ester	mg/dl	114. 2 ± 12. 5 (15)	111. 9 ± 14. 8 (20)	N. S.
Cholesterol/ Cholesterol ester	%	61. 75 ± 3. 16 (15)	60. 91 ± 3. 83 (20)	N. S.
β-/α-lipoprotein		4. 629 ± 1. 456 (10)	3. 889 ± 0. 828 (20)	N. S.
α-lipoprotein	%	11. 630 ± 2. 981 (10)	13. 551 ± 3. 469 (20)	N. S.
β-lipoprotein	%	50. 370 ± 7. 021 (10)	50. 148 ± 6. 802 (20)	N. S.
Preβ-lipoprotein	%	34. 618 ± 7. 259 (10)	31. 807 ± 9. 761 (20)	N. S.

N.B.　( ) mean the number of samples. N.S. not significant. One-tailed Sign Test was applied for the means of the individual samples before and after the drug reduction.

significant changes were observed from this table except body weight and FFA.

Body weight seemed to fall slightly but significantly (after the drug reduction) (p=0.031 by the one-tailed Sign Test). Individual patients' body weight changes are depicted in figure 1, where considerable fluctuations in individual cases may be seen.

The blood levels of FFA were slightly increased after the drug reduction (p=0.031 by the one-tailed Sign Test). It is interesting to observe the individual cases (figure 2) which do not necessarily show an immediate rise after the drug reduction but in whom the rise is gradual and variable.
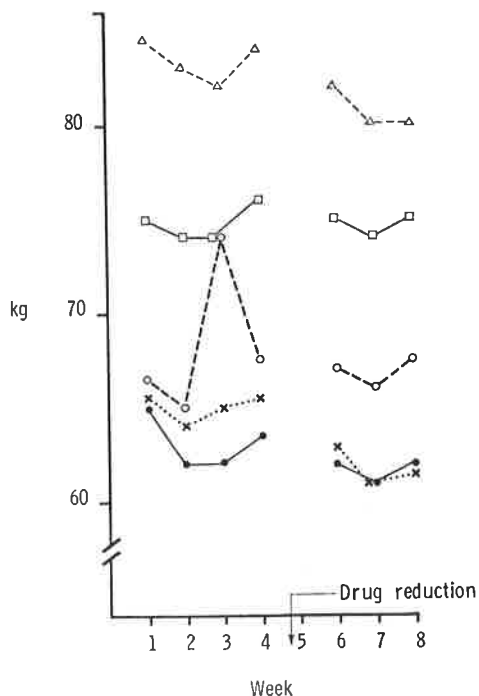
Fig. 1 Body weight of the sample patients be-
fore and after the drug reduction. The
medications were reduced by half in each
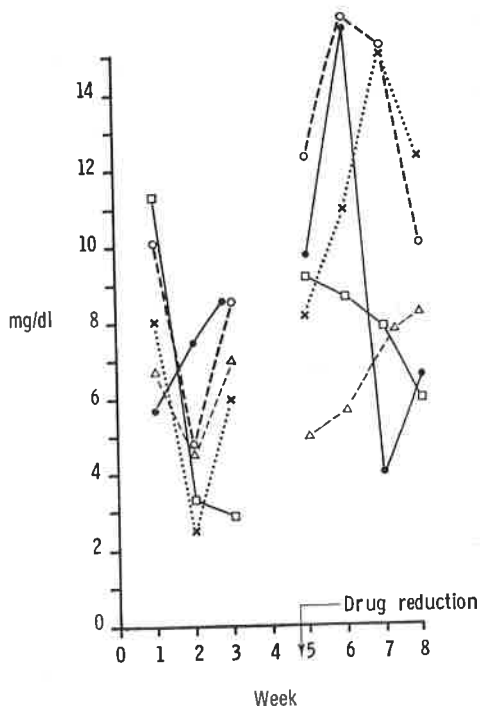case on the day before the fifth sampling.

Fig. 2 Free fatty acids levels of the sample pa-
tients before and after the drug reduction.
The medications were reduced by half in
each case on the day before the fifth
sampling.

DISCUSSION

Overweight is often found among psychiatric patients (*Mefferd et al.* (1958), *Planansky* (1958))
and increases in body weight follow soon after the introduction of neuroleptic administration even when
a consistent diet is maintained (*Sletten and Gershon* (1966)). Some animal experiments have shown
that unlike "hypothalamic obesity", drug-induced obesity is not directly related to food intake (*Mori*
(1970), *Mori* (1971)). This might lead to the assumption that "hypothalamic obesity" is secondary to
overeating caused by a lesion of a brain area associated with satiation whereas drug-induced obesity is
caused by some other variable such as peripheral lipid storage as suggested elsewhere (*Kitamura* (1976)).

The present survey showed that reductions in the dosage of maintenance neuroleptics in chronic
schizophrenics (most of whom were obese) were followed by increases in FFA and decreases in body
weight. This seems to be consistent with the author's hypothesis, though not necessarily contradicting
the "overeating hopothesis".

Increases in FFA, which is normally metabolised very rapidly, were gradual in this study. A pos-
sible explanation for this is that the half life of neuroleptics is usually long and a trace of them may
be found in urine even a year after their withdrawal (*Cowen and Martin* (1968)). Therefore it takes
a relatively long time for excess FFA to be released from adipose tissue.

The present findings are also consistent with a report of *Darwish and Furman* (1977) who have
demonstrated that levodopa produces a dosage-dependent hypoglycaemia response and the rises in FFA
in mice, and that hypoglycaemic responses to levodopa are prevented by haloperidol and pimozide. They
have not, however, mentioned whether the FFA rises are also prevented by dopaminergic antagonists.

This study did not confirm the cholesterol lowering effect of some butyrophenones reported by *Simpson and Cooper* (1966), and *Sobus et al.* (1977). However none of the drugs used by *Simpson and Cooper* was not used in this investigation.

What still remain to be studied are the relationship between food intake and overweight in drug-induced obesity, the identification of physiological system or brain areas which may be related to certain types of obesity, and the separation of peripheral and central actions of neuroleptics.

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向精神薬減量に伴なう代謝及び体重変化に
関する研究（予報）

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東京武蔵野病院において5名の男子慢性分裂病入院患者（内4名は肥満者）より週一日早朝空腹時採血を8回にわたって施行した。採血と同時に体重測定も行われた。5名の平均年令は45才，平均入院期間は18年10ケ月で，精神症状は維持量の向精神薬により安定化され，急性症状は認められなかった。5回目の採血の前日に向精神薬維持量を約半量に減少した。薬用量減少後，血中の遊離脂肪酸の上昇（P＝0.031）及び体重増加（P＝0.031）が認められた。その他の因子——総脂質，リン脂質，中性脂肪，コレステロール，コレステロールエステル，各リポタンパク分画——は正常値内で，向精神薬減量前後の有意な変動はみられなかった。

向精神薬投与にしばしば伴なう肥満は今まで中枢性機序による過食によるものであると言われてきたが，今回の研究の結果，この種の肥満は過食のみならず末梢脂肪組識における脂質過剰によるものであるという著者の仮説の傍証が得られた。