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ABSTRACT

Thirteen chronically institutionalized male psychiatric patients (12 schizophrenics and one general paralysis) werer studied. Blood samples were taken before and after the two-day withdrawal of maintenance neuroleptic treatment. The blood level of prolactin, luteinizing hormone, follicle stimulating hormone, growth hormone, thyrotropin, serotonin, cortisol, immunoreactive insulin, glucose, free fatty acids and triglyceride were estimated. A 50 gramme glucose tolerance test was done before and after the drug withdrawal.

Prolactin was in the normal range before the drug withdrawal and fell to the lower limit of the normal range after. More growth hormone was released in glucose tolerance test after the drug wtihdrawal. No other changes were found before and after the drug withdrawal.

The findings are consistent with the concept of hypersensitivity of the central nervous system (particularly tuberoinfundibular dopaminergic system).

KEY WORDS: Prolaction, Growth Hormone, Major Tranquilizing Agent, Receptor Hypersensitivity

INTRODUCTION

Tardive dyskinesia is often found among those who have been on long term neuroleptics. It has been claimed that this is due to hypersensitivity (supersensitivity) of the dopaminergic receptors in the central nervous system, especially those of the nigrostriatal dopaminergic system (*Gerlach et al.* (1974), *Klawans & McKendall* (1971), *Pare* (1976)). Other dopaminergic neurons in the central nervous system are likely to be similarly affected, including the mesolimbic system (possibly representing psychic phenomena) and tuberoinfundibular system (contributing hormonal equilibrium). One of us has already speculated that the hormonal effects of the withdrawal of neuroleptics are different in acute and chronic medications (*Kitamura* (1976)).

The present survey, therefore, focused on prolactin (PRL) and growth hormone (GH), because both of them are under control of the tuberoinfundibular system and it ts fairly well understood how neuroleptics manipulate the release of these hormones.

MATERIAL

The study group comprised were 12 chronic schizophrenics (I.C.D. 295.6) and one general paralysis, age range from 33 to 62 years old. In order to avoid the hormonal effects caused by menstrual cycles, no females were studied. They had all been residents in the Tokyo Musahino Hospital for more than

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three years (mean±SEM 15.3±9.9 years).

Table 1 Profile of sample population and medication

Patient	Age (year)	Hospitalization (year)	Diagnosis	Prescription (per day)	
1	50	25	S	pipamperone	150mg
				chlordiazepoxide	30mg
				ethopropazine	60mg
				nitrazepam	5mg
				levomepromazine	5mg
2	49	7	S	chlorpromazine	100mg
				perphenazine	20mg
				promethazine	100mg
3	39	18	S	methylperidol	15mg
				levomepromazine	50mg
				promethazine	50mg
4	33	3	S	haloperidol	10mg
				chlorpromazine	200mg
				promethazine	100mg
				biperiden	6mg
				nitrazepam	5mg
				levomepromazine	25mg
5	53	5	GPI	spiperone	3mg
				levomepromazine	50mg
				promethazine	50mg
6	40	5	S	clocapramine	150mg
				biperiden	6mg
				ethylphenylephrine	30mg
7	44	3	S	perphenazine	15mg
				promethazine	30mg
8	52	16	S	carpipramine	150mg
				propericiazine	30mg
				promethazine	75mg
9	53	6	S	chlorpromazine	170mg
				perphenazine	24mg
				carpipramine	150mg
				promethazine	100mg
11	56	28	S	perazine	150mg
				carpipramine	100mg
				carnigen*	3tab
12	44	23	S	prochlorperazine	30mg
				clocapramine	75mg
				promethazine	50mg
				carnigen*	6tab
				ethylphenylephrine	30mg
13	62	25	S	haloperidol	2mg
				nitrazepam	5mg
				ethylphenylephrine	6tab

Patient	Age (year)	Hospitalization (year)	Diagnosis	Prescription (per day)	
14	50	26	S	pipamperone	150mg
				chlorpromazine	150mg
				perphenazine	8mg
				promethazine	50mg

S : Schizophrenia
GPI: General paralysis
* Carnigen® tablet contains nucleosides(equivalent to adenosine 1.2mg) and suprifen hydrochloride 8mg.

Their medications had not been changed for at least 6 months before the start of this survey. All medications were "maintenance" dosage of neuroleptics and a variety of other drugs (Table 1).

All members were weighed and measured. Five were judged obese with reference to *Matsuki*'s standard table for Japanese adults (*Matsuki et al.* (1971)) because they were+10% over the standard weight.

Three patients were found diabetic. The criterion for diabetes mellitus is that of the Japanese Committee on the Criteria of the Oral Glucose Tolerance Test i.e. the venous glucose level above 160mg/dl at 60 minutes, and above 130mg/dl at 120 minutes (*Kuzuya et al.* (1970)).

Continued participation was voluntary, and experimental procedures were fully explained to the patients.

METHODS

The medications were stopped on 2 successive days a week. This procedure was called the "drug holiday" by *Ayd* (1966 and 1967). All examinations but glucose tolerance test (see below) were done on both the first day of the "drug holiday" and the first day of re-starting medication just before taking morning tablets. In the former situation, the medication given in the preceding night was thought to remain in the blood stream, therefore this sample was called the "on drug" sample. On the other hand, in the latter stiuation, blood was taken after 48 hours of withdrawal of medication, therefore this was called the "off drug" sample. The interval of the "on" and "off" drug sampling was 48 hours.

The assays done were the blood level of PRL (*Sinha & Vanderlaan* (1973)), luteinizing hormone (LH), follicle stimulating hormone (FSH), GH (*Utiger et al.* (1962)), thyrotropin (TSH), serotonin (*Thompson et al.* (1970)), cortisol (*Rudd* (1963)), immunoreactive insulin (IRI) (*Morgan & Lazarow* (1963)), glucose (*Somogyi* (1945)), free tafty acids (FFA) (*Itaya & Kadowaki* (1969)), triglyceride (TG) (*Fletcher* (1968)), and 50 gramme glucose tolerance test (GTT). In the GTT, blood samples were taken 0, 30, 60 and 120 minutes after 50 gramme of oral glucose load, and the blood level of glucose, FFA, TG, IRI, and GH were assayed. It should be mentioned here that the morning medication was given before the GTT on the day of the "on drug" sampling (i.e. the first day of the "drug holiday") while it was given after the GTT on the day of the "off drug" sampling (i.e. the first day of re-starting medication).

The samples for PRL, LH, FSH, GH, TSH, serotonin, cortisol, and IRI were frozen until assayed at Kitasato Biochemical Laboratory. Other factors were assayed at the Department of Biochemistry, Institute of Psychiatry Tokyo immediately after the samplings.

RESULTS

The blood PRL level of the "on" sample was 7.08±8.12 ng/ml (mean±SEM) and that of the

Table 2 Blood levels of hormones before ("on" sample) and after ("off" sample) two-day withdrawal of maintenance neuroleptics N.S. not significant

	"ON" SAMPLE	"OFF" SAMPLE	NORMAL RANGE	TWO-TAILED WALSH TEST
PROLACTIN	7.08±8.12 (13)	2.20±2.62 (13)	2−20ng/ml	p=0.01
LUTEINISING HORMONE	14.75±8.40 (13)	11.78±6.36 (13)	6.5−34.5mIU/ml	N. S.
FOLLICLE STIMULATING HORMONE	16.96±14.01 (13)	16.95±10.52 (13)	1.9−21.8mIU/ml	N. S.
THYROTROPIN	3.40±2.88 (5)	2.60±1.52 (5)	<12μU/ml	N. S.
SEROTONIN	11.15±7.32 (13)	10.17±5.98 (13)	10−30μg/dl	N. S.
PLATELET	208, 600±51, 700 (13)	219, 500±45, 200 (13)	170, 000−333, 000/μl	N. S.
SEROTONIN/PLATELET	53.8±35.9 (12)	54.4±25.7 (11)		N. S.
CORTISOL	14.02±6.16 (13)	15.39±3.37 (13)	4.5−15.3μg/dl	N. S.

( ) sample number

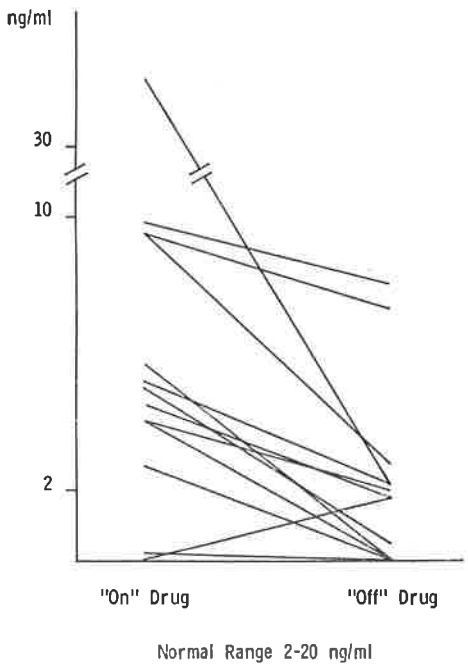

Fig. 1. Blood prolactin level before ("on" drug) and after ("off" drug) two-day withdrawal of maintenance neuroleptics. Each line represents one patient.

"off" sample was 2.20±2.62 ng/ml (Table 2). Since the normal range of blood PRL is 2-20 ng/ml, the "on" sample level was in the normal range but the "off" sample level was decreased to the lower limit of the normal range with significance (p=.01 by the two-tailed Walsh test). The individual cases are shown in the figure 1 and it is noteworthy that the case which showed the highest PRL level of the "on" sample (32.0 ng/ml) was that of general paralysis.

No change between the "on" and "off" drug samples was found as far as LH, FSH, TSH, serotonin, serotnin/platelet ratio, and cortisol were concerned (Table 2).

There was no difference of glucose, FFA, TG, IRI, and GH between "on" and "off" samples. And the initial values in GTT of these factors showed no significant difference between the "on" and "off" samples. Even when the values of the single sampling and the initial value of GTT were calculated together, it did not, again, show any significant difference between the "on" and "off" samples (Table 3).

Therefore, the fluctuations of these items during

Table 3 The levels of glucose and other related factors before ("on" sample) and after ("off" sample) two-day withdrawal of maintenance neuroleptics

		GLUCOSE	FFA	TG	IRI	GH
"ON" SAMPLE	SINGLE SAMPLING	105.2±15.4 (20)	11.10±5.13 (20)	144.1±36.2 (19)	11.8±7.6 (20)	0.95±0.68 (20)
	INITIAL VALUE OF GTT	105.2±10.6 (12)	10.66±5.84 (12)	148.6±63.3 (12)	12.3±7.6 (12)	1.06±0.46 (12)
	TOTAL	105.2±13.6 (32)	10.93±5.31 (32)	145.9±47.5 (31)	12.0±7.5 (32)	0.99±0.60 (32)
"OFF" SAMPLE	SINGLE SAMPLING	106.3±19.5 (18)	9.47±4.58 (18)	138.9±34.9 (18)	11.1±6.6 (18)	1.37±1.27 (18)
	INITIAL VALUE OF GTT	96.2±7.5 (13)	9.58±5.43 (13)	148.4±51.1 (13)	10.7±5.2 (13)	1.13±1.16 (13)
	TOTAL	102.1±16.2 (31)	9.52±4.87 (13)	142.9±41.9 (31)	10.9±5.9 (31)	1.26±1.21 (31)
NORMAL RANGE		70—120mg/dl	10.0—15.4mg/dl	70—120mgdl	7—24μU/ml	2—20ng/ml

( ) sample number

GTT were compared in the "on" and "off" drug samples. It was defined in this survey that "rise" means the difference between the maximum level during GTT and the initial level (negative if the latter is higher than the former) and a "fall" means the difference between the initial level and minimum level during the GTT. There were no significant fluctuation changes between the "on" and "off" samples as far as glucose, FFA, TG, and IRI were concerned. However, GH "rise" was higher "off" drug than "on" drug ($p=0.31$ by the one-tailed Walsh test) though GH "fall" was the same in the "on" and "off" samples (Fig. 2).

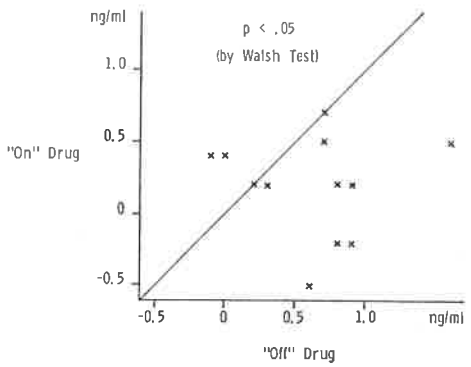

Fig. 2. Growth hormone "rise" during GTT before ("on" drug) and after ("off" drug) two-day withdrawal of maintenance neuroleptics. The dividing line separates "rises" that were higher after the drug withdrawal (below the line) from those which were higher before the drug withdrawal. Each cross represents one patient.

DISCUSSION

It has been generally established that GH is released by insulin-induced hypoglycemia and this phenomenon is inhibited by chlorpromazine (CPZ) (*DeWied* (1967), *Saldanha et al.* (1972), *Sherman et al.* (1971)), though some investigators have observed no GH release supression by neuroleptics, (*Brambilla et al.* (1975)). This controversy is at least partially derived from the dosage of neurolep-

tics used for supression. For example, *Brambilla* and his colleagues have observed no inhibiting effects upon GH release by the administration of 6mg of haloperidal whereas *Saldanha* and his co-workers have found an inhibiting effect by 300mg daily of CPZ.

It has not yet been thoroughly studied whether CPZ or other neuroleptics have potency to change the pattern of GH release during hyperglycemia. A study done by *Benjamin et al.* (1969) has shown that GH release during a six-hour GTT is repressed among patients with thioridazine-induced galactorrhoea, but not among those patients of other types of galactorrhoea who were apparantly on no neuroleptics.

The present investigation showed no significant change of pattern of blood levels of GH related factors between the "on" and "off" samples, except for a GH "rise" during GTT which seemed to be significantly blocked by medication. This would suggest that the medications given to the sample patients were still working as dopaminergic blockers because GH is mainly released by dopaminergic stimuli (*Brown et al.* (1973), *Imura et al.* (1972), *Lal et al.* (1972)).

The change of PRL level due to acute administration of neuroleptics has been studied by many investigators (*Beaumont et al.* (192), *Costa et al.* (1975), *Gruen et al.* (1975), *Gruen et al.* (1978), *Kleinberg et al.* (1971), *Kleinberg & Frantz* (1971), *Meltzer et al.* (1975), *Meltzer et al.* (1976), *Sachar et al.* (1975), *Sachar et al.* (1977), *Sulman et al.* (1956), *Turkington* (1912)). The PRL level is increased by the blocking of prolactin inhibiting factor which is sensitive to dopaminergic stimuli or is dopamine itself. This blocking phenomenon is caused by the dopaminergic blocking potency of neuroleptics.

The change of blood PRL level due to chronic administration of neuroleptics has rarely been studied, although *Van Praag* (1977) has mentioned a study of administration of medication for 6 months, where PRL level remains as high as in the acute stage.

The PRL level of unmedicated schizophrenics both acute and chronic has been studied by a few researchers. *Meltzer et al.* (1974 a) have demonstrated that 16 acute schizophrenics' level is 5.5 ± 2.8 ng/ml,5 chronic patients' level is 8.3 ± 3.8 ng/ml (totally 6.0 3.2 ng/ml.). *Kolakowska et al.* (1975) have shown 24 ± 10 ng/ml as the prolactin level of 14 unmedicated schizophrenics. *Johnstone et al.* (1977) have measured PRL in 16 schizophrenics twice with an 8 week interval and the values were 11.6 ± 6.9 ng/ml and 10.3 ± 5.8 ng/ml.

The withdrawal effects of neuroleptics upon PRL has been studied by *Meltzer et al.* (acute medication) (1976) and *Beumont et al.* (chronic medication) (1974 a & b). *Meltzer et al.* have observed that the serum PRL level rapidly reverts from the elevated value to normal within 48 to 96 hours after cessation of phenothiazines. On the other hand in *Beumont's* study, it seems that the PRL level is within the normal range "on" drug, and is decreased "off" drug although they have not, unfortunately, shown statistical analysis.

The present study showed that PRL level was in the normal range "on" drug, and fell to the lower end of the normal range after the "drug holiday", and furthermore it was decreased to zero level in three cases. This change was specific to PRL because no change was observed between the "on" and "off" drug samples of the gonadotropins. The possible influence of serotonin and TRH, which may, to some extent, alter the level of PRL (*Meltzes et al.* (1974 b)), were not shown to do so in this survey. Hence it is speculated that small amount of neuroleptics have some effects on PRL which is, however, different from that due to the withdrawal of acute medication. If the mechanism here were the same as that in the withdrawal of acute medication, then the PRL level should be higher than normal range. If the normal value of the "on" drug PRL level were caused simply by the small and insufficient dosage of neuroleptics, then no change (of both PRL and GH) should occur after the dis-

continuation of neuroleptics. The concept of hypersensitivity would be consistent with the present findings.

The findings here might be due to the nature of this survey as an open trial. The patients knew that medication was not given between "on" and "off" samples, therefore they may have been psychologically more alert. However psychological stress normally tends to increase the PRL level (*Noel et al.* (1972)), while in this study PRL level was decreased after the "drug holiday". Psychological stress also increases adrenal cortical activity (*Fishman et al.* (1962), *Mason et al.* (1965), *Sachar et al.* (1966), *Tolson et al.* (1965), *Rubin & Mandel* (1966)), but no difference of the cortisol level was found between the "on" and "off" sample in this survey. Hence it is speculated that any possible psychological factor is negligible.

If this hypothesis were the case, it would be clinically suggested that in those patients who already have dopaminergic hypersensitivity in the tuberoinfundibular, the negrostriatal, and presumably the mesolimbic systems, the long term maintenance dosage of neuroleptics has no relapse preventative potency, but has an adverse effect to provoke relapse when discontinued, because withdrawal of maintenance neuroleptics will cause dopaminergic hyperactivity and dopaminergic stimuli such as L-DOPA administration my provoke a psychotic episode (*Angrist et al.* (1973)). However, as far as the sample patients of this survey were concerned, no relapse or deterioration was observed during the experimental period. And this hypothesis is based on the simplified asumption that the activities of variety of dopaminergic pathways are possitively correlated. This is the point of the current discussion and remains to be studied.

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長期服用抗精神薬の中止の内分泌への影響

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抗精神病薬の作用機序として，中枢神経系内ドーパミン作働性ニューロンへの影響が考えられているが，その作用は急性投与．慢性投与，長期投与後の休薬などによって異なる。本研究は，ドーパミン系の主要な1つである結節—漏斗系で調整されているプロラクチンと成長ホルモンに焦点をあて，それらの放出が抗精神病薬慢性投与と休薬とでどのように変化するかみたものである。

対象は13例（精神分裂病12例，進行麻痺1例）の長期入院男性患者で，採血を抗精神病薬長期維持量服用中の2日間休薬の前後に行ない，プロラクチン，黄体形成ホルモン，卵胞刺激ホルモン，成長ホルモン，甲状腺刺激ホルモン，セロトニン，コルチゾーン，インシュリン，ブドウ糖，遊離脂肪酸，中性脂肪の血中濃度を測定した。50g糖負荷試験も休薬の前後に行なわれた。

プロラクチンは休薬前は正常範囲の値を示すが，休薬後には正常値の下限に減少する。糖負荷試験における成長ホルモン放出は休薬後により亢進する。それ以外の測定値には休薬前後で変化が認められなかった。

以上の結果は抗精神病薬による中枢神経系（特に結節・漏斗ドーパミン作働系）の過感受性の考えを裏づけるものである。