

## EFFECTS OF DAILY CHLORPROMAZINE ADMINISTRATION ON BEHAVIOURAL AND PHYSIOLOGICAL PARAMETERS IN THE RAT

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**Abstract :** Chlorpromazine is a classical neuroleptic drug which produces both therapeutic effects as well as unwanted side effects in human such as sedation, autonomic, endocrine and neurological effects.

It is thought that blockade of dopamine D-2 receptors caused by chlorpromazine induces these untoward side effects. Pre-clinical studies on catalepsy has been proposed as an animal model for neuroleptic induced extrapyramidal side effects.

The drug also blocks certain stereotypic behaviours in animals induced by dopamine agonists such as apomorphine and amphetamine. These stereotypic behaviours are circling, chewing, rearing, grooming and hyperactivity. Daily administration of chlorpromazine (1, 3 and 10 mg/kg, i.p) to rats for 21 days induced catalepsy, tolerance to catalepsy and locomotor sensitization following PCP (10 mg/kg, i.p) challenge.

These results suggest that daily chlorpromazine treatment induced DA/NMDA-receptor sensitization to total locomotor activity following PCP challenge. Furthermore, there were no changes in other behavioural parameters assessed. Surprisingly daily chlorpromazine administration in rats also produced no changes in other physiological parameters assessed (body weight, food and water intake).

**Key words :** chlorpromazine      stereotyped behaviours      catalepsy  
locomotor activity      neuroleptic      extrapyramidal effects

### INTRODUCTION

In 1952, an experimental drug which had therapeutic effects in the treatment of schizophrenia was introduced. This neuroleptic drug was named as

chlorpromazine (1).

Chlorpromazine as a classical neuroleptic drug produces both therapeutic “effects as well as unwanted side effects. These unwanted effects include sedation,

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haematological, autonomic, endocrine and neurological effects. Furthermore, these effects can occur depending on the dose administered and the duration of treatment (2). The occurrence of these symptoms in patients varies with time and several symptoms show overlap (3).

It is thought that blockade of dopamine D-2 receptors in the basal ganglia caused by chlorpromazine induces these untoward effects (4). Pre-clinical studies on catalepsy has been proposed as an animal model for neuroleptic induced extrapyramidal (EPS) side effects (5–6).

Chlorpromazine blocks certain stereotypic behaviours in animals induced by dopamine agonists like apomorphine and amphetamine, such as circling, chewing and hyperactivity (7–8). These behaviours are thought to occur due to activation of dopamine receptors located post-synaptically (9). Other apomorphine induced effects such as hypothermia and hypoactivity are proposed to be due to stimulation of pre-synaptic dopamine receptors. These effects have been shown to be blocked by some neuroleptic drugs (9).

Classical neuroleptics like chlorpromazine have antipsychotic actions and have been suggested to increase brain DA turnover due to compensatory feedback mechanisms in response to blockade of DA-receptors (10). The drug also produces sedative effects and hypothermia because it acts on other receptor system besides the dopaminergic system: it antagonizes alpha-adrenergic receptors (11), 5-HT-receptors (12), histaminic ( $H_{-1}$ ) and muscarinic ( $M_{-1}$  &  $M_{-2}$ ) receptors (13).

It has been reported that chronic treatment with neuroleptics like chlorpromazine causes super-sensitivity of dopamine receptors, as well as behavioural super-sensitivity of dopamine agonists (14). Thus, there is an increase in number and super-sensitivity occurring at the dopaminergic receptors. Development of tolerance induced by chlorpromazine is usually a consequence of supersensitivity of DA receptors (15). When neuroleptics are administered acutely to animals, these drugs block the effects of dopamine agonists (16). Both in man and animals tolerance has been reported to develop to some behavioural effects of neuroleptics (17–18).

The present study assessed whether daily chlorpromazine administration would cause sensitization or tolerance to various behavioural (locomotor activity, stereotypies, catalepsy and colonic temperature) and suppressant effects/physiological parameters (body weight, food consumption and water intake) following daily chlorpromazine treatment (1, 3 and 10 mg/kg, ip) for 21 days.

#### MATERIALS AND METHODS

One hundred thirty two (132)-Male Sprague-Dawley rats were obtained from Harlan Olac, Bicester, U.K. (weight on arrival: 200–250 g). Animals were housed 4 per cage in plastic bottomed cages, and left for one week to acclimatize before the start of the experiment. Animals were allowed free access to food and water.

Following a one week acclimatization period, 36 rats out of 132 were selected based on their weights and were singly housed two

days prior to the start of the experiment and were left in the treatment room to acclimatize to the condition.

These animals were then allocated to 4 groups: 12 animals as controls and 3 groups of 8 animals per group respectively, which were singly housed during the daily chlorpromazine dosing. Chlorpromazine was prepared as a 10 mg/ml solution in saline containing 0.25% Tween 80. Subsequent dilutions of 1 and 3 mg/ml were made and administered daily intra-peritoneally to animals between 10.00 and 11.00 am. Chlorpromazine, d-amphetamine hydrochloride and apomorphine hydrochloride were obtained from Sigma Chemicals Co, U.K. Phencyclidine (PCP) hydrochloride was obtained from Plaistow, Cork, Ireland.

PCP was prepared as a 10 mg/ml solution in saline, and was administered intra-peritoneally to all animals on day 17 as a challenge. Amphetamine was prepared as a 5 mg/ml solution in saline and was administered intra-peritoneally to all animals on day 19 as a challenge. Apomorphine was prepared as a 1 mg/ml solution in saline containing 0.5% ascorbic acid, and was administered subcutaneously to all animals on day 21 as a challenge. All challenges were given between 10.00 and 11.00 am.

#### Home cage activity

Throughout the study, animals were singly housed in plastic bottomed cages. During challenge days, cages were placed in racks which had infra-red sensors attached (30 min before drug challenge). The effects

of daily chlorpromazine treatment were measured on each challenge day using the home cage activity monitor for saline, PCP, amphetamine and apomorphine.

Monitoring commenced at 10.30 am on each challenge day. Observation of stereotyped behaviours was observed 30 min after the drug challenge. Cages were placed in racks to which infra-red sensors were attached enabling locomotor activity to be measured for the period of 4 hrs for saline and PCP, and 2 hrs for amphetamine and apomorphine. These time difference between PCP and amphetamine and apomorphine was set because of the difference in half lives as it is short for the apomorphine (40 minutes), amphetamine (10–13 hrs) and PCP (7–48 hrs) (19), whereas saline was used as a control where animals behave the same all the time regardless of the duration of observation time. After each challenge day, the animals were removed from the monitor and returned to the holding room, and injected with chlorpromazine.

Fresh chlorpromazine was prepared every morning throughout the study period. Two days (48 hrs) was allowed as a wash out period for PCP, amphetamine and apomorphine as this was earlier thought to be enough period based on their rate of metabolism in the animals body. However, later on it was found that this washout period of 48 hrs was not adequate because PCP and amphetamine have long half lives and this means a substantial amount of the drugs in the body was left and as a result these two drugs (PCP and amphetamine) could have had a residual effects on apomorphine challenge.

### Stereotyped behaviours

The stereotyped behaviours observed and recorded were: grooming, rearing, chewing, turning, vertical head movements, exploratory movements, head rolling, falling and ataxia. The scores for each behaviour were either "0" for absence or "1" for presence of a particular behaviour during a 1 min observation period for each rat. All observations for these stereotyped behaviours were made whilst the animals were in their home cage. The sum of a single observation was taken and values recorded.

### Data analysis

A analysis of variance (ANOVA) test was performed on body weights, food consumption, water intake and temperature data. If any significant changes were found, the data was analysed using Student's-t-test. Results are tabulated as group means,

standard errors of the means (SEM), and coefficient of variation (C.V. = standard deviation/mean, expressed as a percentage).

Initially, the Kruskal Wallis test was performed on home cage locomotor activity, stereotyped behaviour and catalepsy (block test) data. If statistically significant changes were found, the data were further analyzed using a Mann-Whitney-U-test. Results are tabulated as group medians and inter-quartile range (Q1-Q3).

## RESULTS

### Effects of PCP, saline, amphetamine and apomorphine challenges on home cage locomotor activity (Fig. 1):

PCP challenge produced a significant increase in total locomotor activity in the 3 and 10 mg/kg groups of daily chlorpromazine treated animals ( $P < 0.05$  and  $P < 0.01$  vs control respectively).

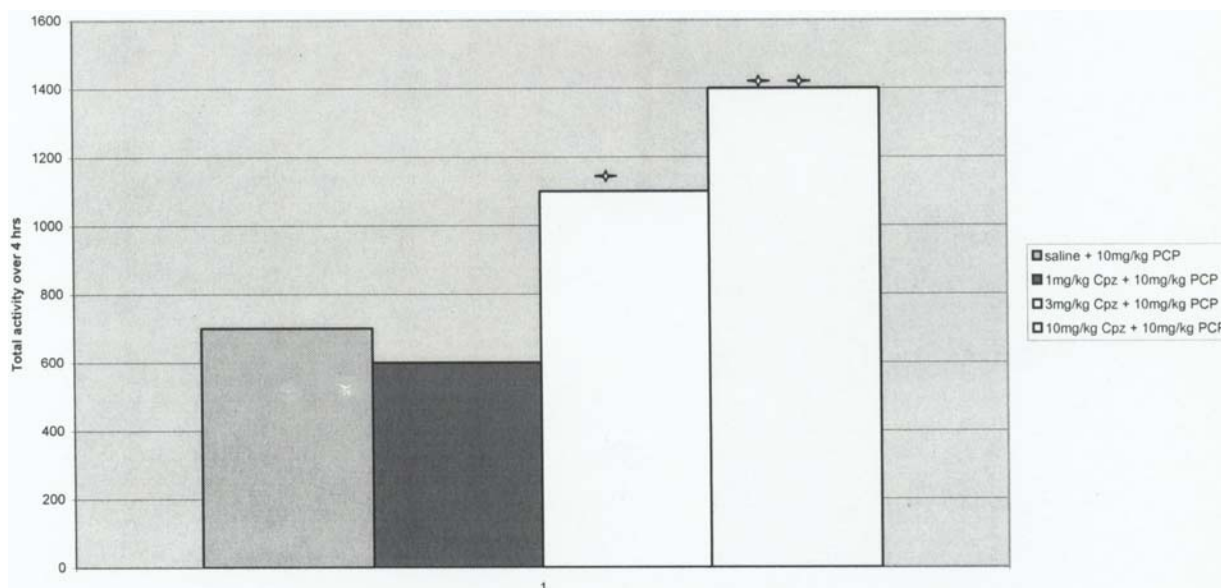


Fig. 1: Effects of PCP challenge on home cage locomotor activity. Home cage activity was measured 24 hrs following last dose of chlorpromazine and immediately following PCP (10 mg/kg) for 4 hrs. Results are expressed medians. \*= $P < 0.05$ , \*\*= $P < 0.01$  vs controls.

Saline challenge to daily chlorpromazine treated animals, no effect on total activity occurred; the lower dose group showed a slight increase in locomotor activity. Similarly, amphetamine and apomorphine challenges had no effect on locomotor activity in daily chlorpromazine treated animals.

**Effect of challenges on behavioural parameters in daily chlorpromazine treated animals (Table I):**

Saline challenge had no effect on

behavior. PCP challenge also had no effect on behaviors, though the head rolling behaviour was increased in the high dose chlorpromazine group (10 mg/kg) which was significant (P<0.05 vs control).

The amphetamine challenge had little effect on behaviours. The apomorphine challenge showed no overall effect on behaviours, whilst chewing behavior showed a slight increase in all 3 chlorpromazine treated groups.

TABLE I: Effects of challenges (with saline, PCP, amphetamine and apomorphine) on stereotyped behaviour following daily chlorpromazine administration in the rat.

<i>Drug challenge</i>	<i>Groom median (Q1-Q3)</i>	<i>Rearing median (Q1-Q3)</i>	<i>Chewing median (Q1-Q3)</i>	<i>Turning median (Q1-Q3)</i>	<i>Vertical head movement</i>	<i>Extrapyramidal movements (Q1-Q3)</i>	<i>Circling median (Q1-Q3)</i>	<i>Head rolling median (Q1-Q3)</i>
Saline								
Control	0 (0-0)	2 (0-4)	0 (0-0)	-	-	-	-	-
1 mg/kg								
Cpz	0 (0-0)	0 (0-4)	0 (0-0)	-	-	-	-	-
3 mg/kg	0 (0-0)	0 (0-0)	0 (0-0)	-	-	-	-	-
10 mg/kg	0 (0-0)	0 (0-0)	0 (0-0)	-	-	-	-	-
10 mg/kg PCP								
Control	0 (0-0)	0 (0-0)	0 (0-0)	-	-	-	1 (0-2)	29 (25-30)
1 mg/kg								
Cpz	0 (0-0)	1 (0-5)	2 (0-4)	-	-	-	2 (0-4)	25 (20-30)
3 mg/kg	0 (0-0)	0 (0-0)	0 (0-0)	-	-	-	3 (2-5)	31 (23-30)
10 mg/kg	0 (0-0)	0 (0-0)	0 (0-0)	-	-	-	4 (1-6)	48 (24-62)*
5 mg/kg amphet								
Control	0 (0-0)	3 (0-6)	0 (0-0)	2 (0-5)	48 (0-55)	13 (0-25)	-	-
1 mg/kg								
Cpz	0 (0-0)	4 (0-11)	0 (0-0)	19 (0-24)	34 (23-56)	3 (0-5)	-	-
3 mg/kg	0 (0-0)	3 (0-5)	0 (0-0)	10 (0-23)	50 (2-67)	8 (0-20)	-	-
10 mg/kg	0 (0-0)	0 (0-0)	3 (0-7)	13 (6-41)	0 (0-0)	0 (0-0)	-	-
1 mg/kg Apo								
Control	0 (0-0)	0 (0-0)	37 (26-50)	6 (0-7)	4 (0-10)	0 (0-0)	-	-
1 mg/kg								
Cpz	0 (0-0)	0 (0-0)	35 (29-46)	0 (0-0)	0 (0-0)	0 (0-0)	-	-
3 mg/kg	0 (0-0)	0 (0-0)	40 (29-50)	4 (0-5)	1 (0-6)	0 (0-0)	-	-
10 mg/kg	0 (0-0)	0 (0-0)	41 (23-56)	2 (0-5)	0 (0-0)	0 (0-0)	-	-

Results are expressed as total median counts 30 minutes following challenges with saline, PCP, amphetamine and apomorphine on days 16, 17, 19 and 21. Results in parenthesis are the interquartile range (Q1-Q3). \*=P<0.05 vs control.

## DISCUSSION

**Chlorpromazine produces blockade at DA-D<sub>2</sub> and 5-HT receptors (12):** This drug interacts with dopaminergic, muscarinic, serotonergic, as well as other receptors (13). Leysen et al. (21–22), proposed that both DA and 5-HT receptors are involved in the mechanism of action of antipsychotic effects.

At doses employed in this study, chlorpromazine had no effect on body weight, food and water intake. However, other researchers have reported a decrease in body weight, food consumption or fluid intake after such treatments (23–24). Such changes were not noted in the present study. Furthermore, the present results are in conflicts with others (3) because chlorpromazine and other typical neuroleptics produces weight gain in man as the drugs induces excessive eating while individuals are on treatment. That means some neuroleptics if not all increase appetite in man. These discrepancies in our study are not known at present, but could possibly be due to differences in experimental conditions/setting, environmental, duration of the study, doses used, routes of drug administration and animal species versus man, as all of which can produce variabilities (25).

However, further studies are needed to establish whether the cause of weight gain in humans is due to endocrine changes because of neuroleptics or being secondary because of their improved mental state after treatment. It has been reported that these D-1 and D-2 receptors stimulate growth hormone release (26).

Furthermore, chlorpromazine administration was withheld on PCP, Apomorphine and amphetamine challenge days, this was a design issue as co-administration causes drug competition/antagonism for DA receptors. Behavioural and total activity suppression in this study following saline, amphetamine and apomorphine challenges have been reported previously by Fibiger et al. (25), but not Theodorou et al. (14). Thus, there are always an increase in number and super-sensitivity occurring at the dopaminergic receptors. Furthermore, development of tolerance induced by daily chlorpromazine administration is usually a consequence of super-sensitivity of DA receptors (15). The present results show that no DA receptor super-sensitivity developed over the 2 weeks period of daily chlorpromazine treatment before challenges were given. However, in this study the number of receptors (DA-receptor upregulation or an increase in the number of DA-receptors) was not determined. Furthermore, Rupniak et al. (16, 26), have reported a DA receptor sub-sensitivity following chronic neuroleptic administration and this conflicts with results of this study and the previous findings (14). This could be due to differences in methodology and settings of the actual period of calling and measuring chronic administration as this may differ between studies.

Chlorpromazine has a weaker activity at pre-synaptic DA-receptors as it fails to reverse apomorphine induced sedation and hypoactivity (27). Furthermore, chlorpromazine causes sedation and hypothermia in rodents (18), and reduces

activity in animals and man (28). Repeated treatment of rats with a dopamine antagonist like haloperidol, also produces behavioural supersensitivity to dopamine agonists like apomorphine (29–30). This increased supersensitivity to dopamine appears to be mediated in part by an increased number (upregulation) of DA receptors (29, 31). In contrast, the exact mechanisms underlying behavioural sensitization following repeated/daily or chronic agonist administration are still not known (32). It is also possible that the results observed after the challenges with PCP and amphetamine despite giving a washout period of 2 days still there could be some residual effects remaining which contributed to some of these observed findings.

It therefore seems that chlorpromazine had no effects on pre-synaptic dopaminergic receptors. Thus, certain behavioural effects that are mediated by chlorpromazine may be due to its direct action on DA receptors, whilst others may be due to an indirect action exerted on other systems (33). Its antipsychotic action are thought to be solely due to D-2 blockade (34). Further support comes from Carlsson and Lindqvist (35), as they reported that chlorpromazine has effects on DA, as well as noradrenergic systems and enhances synthesis and utilization of serotonin (36).

In this study, PCP challenge caused an increase in total locomotor activity and head rolling in the high dose chlorpromazine treated group. This drug has the ability to activate other receptors (causing supersensitivity) besides the dopaminergic system (37), such as the serotonergic (38),

and the NMDA-receptors (39). However, there are contradictions as some have reported that PCP is an NMDA receptor agonist (39), whereas, Kapur and Seeman (40) reported that PCP and Ketamine are NMDA antagonists. Ataxia is a common feature which follows PCP administration to rodents (41). This response was observed in animals following PCP challenge, and could explain why total activity and other behavioural parameters were not increased following the PCP challenge. These findings of the inability of chlorpromazine to block completely PCP-induced activity and head rolling in the highest dose are in conflict with Freed et al. (42), who reported that chlorpromazine was effective in blocking PCP-induced hyperactivity.

In the present study, the highest dose of chlorpromazine (10 mg/kg), induced hypothermia. It has been reported as well by others that chlorpromazine induces hypothermia and sedation in rodents due to blockade of DA, 5-HT and alpha-one-adrenergic receptors (18, 43). Others however, have reported that classical neuroleptics do not induce hypothermia (44), such finding are again in conflict with ours. The reason for the difference can not be fully explained but needs further research investigations in this area to establish the actual cause.

An apomorphine challenge in daily chlorpromazine treated rats produced hypothermic responses. These findings are in agreement with other authors for the effects of apomorphine in humans (45), and animals (46–47). Both DA and 5-HT<sub>1A</sub> receptors are thought to be involved in thermoregulation responses in rats (48–49).



Both DA and 5-HT<sub>1A</sub> receptors are thought to be involved in thermoregulation responses in rats (46–47).

In conclusion, the present study demonstrates that DA/NMDA-receptor sensitization developed to total locomotor activity following PCP challenge. Furthermore, there were no changes in other behavioural parameters assessed. Surprisingly daily chlorpromazine administration in rats also produced no changes in other physiological

parameters such as body weight, food and water intake.

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