

# EFFECT OF DRUGS INFLUENCING SYNTHESIS OF PROSTAGLANDINS ON HALOPERIDOL-INDUCED CATALEPSY IN RATS

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( Received on May 31, 1984 )

**Summary :** Rats pretreated with prostaglandin synthesis stimulators, phenoxymethyl penicillin (2, 4 and 8 mg/kg, ip) and levamisole (2.5, 5 and 10 mg/kg, ip) showed a dose related potentiation of catalepsy after subthreshold doses of haloperidol (0.1 mg/kg, ip). Pretreatment with prostaglandin synthesis inhibitors paracetamol and indomethacin exhibited significant inhibition of catalepsy at lower doses (2.5, 5, 10 and 15 mg/kg, ip). However, this antagonism was paradoxically less at higher dose levels (20 and 30 mg/kg, ip). The data suggest neuromodulatory contribution of prostaglandins in neuroleptic-induced catalepsy.

**Key words :** haloperidol

catalepsy

PG synthesis blockers

PG synthesis stimulators

prostaglandins

## INTRODUCTION

Neuroleptics produce catalepsy in animals by blocking dopamine receptors (7). Central dopamine receptor blockade increases prolactin secretion (5, 10, 11). Available evidence suggests that prolactin acts by increasing synthesis of prostaglandins (PGs) in the target organs (13, 14). Since PGs modulate transmission in catecholaminergic neurones (1) it was thought worthwhile to investigate on neuroleptic-induced catalepsy the effect of drugs that alter brain PG levels.

## MATERIAL AND METHODS

Male albino rats, 180–220 g housed at 27–32°C and with free access to standard diet and tap water were used. Experiments were conducted between 10 and 16 hrs. Catalepsy was assessed by placing the animal's two front paws on a horizontal bar positioned 7.5 cm above the floor and measuring the time in seconds, before the animal placed one or both paws on the floor (descent latency time). A maximum of 300 sec was allowed for each animal (12). Six animals were taken in each group and catalepsy

was assessed at one hour intervals for 4 hours. Each rat was used once only. Student's unpaired 't' test was used for statistical analysis.

Haloperidol (Searle) injection solution was diluted to required strength with distilled water. Phenoxymethyl penicillin (Pfizer) was dissolved in distilled water. Indomethacin (IDPL) and paracetamol were dissolved in alkaline solution (pH 8.2–8.5) and final volume was made by adjusting the pH (7.5). Few drops of methanol in distilled water were used to dissolve levamisole. All drugs were injected intraperitoneally; prostaglandin synthesis inhibitors were injected 30 min prior to haloperidol. The control group received equal volume of vehicle ip 30 min before receiving haloperidol. The threshold and subthreshold dose of haloperidol for catalepsy was determined in separate series of experiments keeping saline treated animals as control.

## RESULTS

With subthreshold dose of haloperidol (0.1 *mg/kg*) using six animals in each group, the highest mean descent latency time 21.6 and 20 sec was obtained at 2 and 3 hr respectively. The mean descent latency time in saline control group was 15 sec. Pretreatment with phenoxymethyl penicillin (2, 4 and 8 *mg/kg*) and levamisole (2.5, 5 and 10 *mg/kg*) produced potentiation ( $P < 0.01$ ) of haloperidol effect in a dose related manner (Fig. 1). The cataleptic effect of high dose of neuroleptic (3 *mg/kg*) was anta-

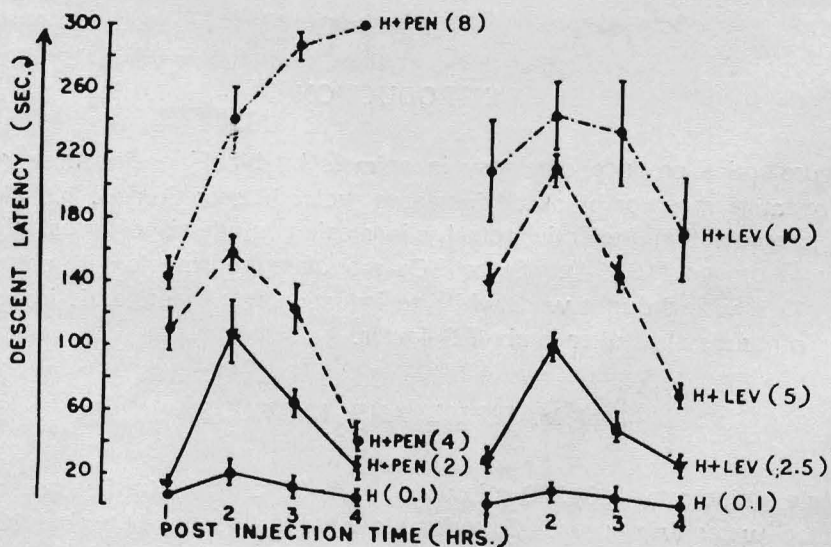


Fig. 1 : Effect of pretreatment with graded doses of penicillin (PEN) and levamisole (LEV) on catalepsy (Descent latency time) induced by subthreshold doses of haloperidol (H).

(Figures in parentheses indicate doses in *mg/kg*. Each point represents mean of 6 animals. Vertical bars denote  $\pm$  S.E.M.)

gonised by prostaglandin sythesis inhibitors but there was no consistent dose relationship. Higher doses showed less antagonism (Fig. 2). Prostaglandin synthesis stimulators or inhibitors perse were devoid of any effect on descent latency time.

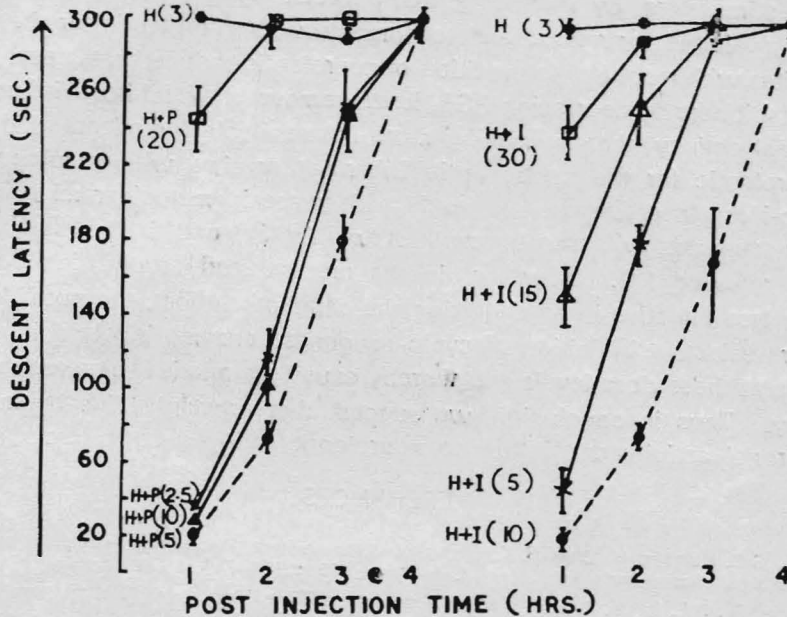


Fig. 2 : Effect of pretreatment with graded doses of paracetamol (P) and indomethacin (I) on haloperidol (H) induced catalepsy.

(Figures in parentheses indicate doses in mg/kg. Each point represents mean of 6 animals. Vertical bars denote  $\pm$  S.E.M.)

### DISCUSSION

Antipsychotic effect of neuroleptics and their ability to produce catalepsy in animals have been related to decrease in striatal dopaminergic activity (7). Most of the drugs stimulate prolactin release which in turn stimulate PG synthesis (9, 13). PGE<sub>1</sub> is known to induce catalepsy in large doses (15). Indirect evidence to implicate central PGE<sub>1</sub> deficiency in pathogenesis of schizophrenia are available (8, 9). Penicillin (PGE<sub>1</sub> stimulator) given orally markedly improved chronic schizophrenia (9). Zinc and penicillamine (PGE<sub>1</sub> stimulators) have also been reported to improve these patients (6, 9). On the other hand paranoid psychosis with indomethacin is also well documented (4).

Phenoxymethyl penicillin and levamisole mobilize dihomogamalinolinic acid and thereby increase prostaglandin E<sub>1</sub> synthesis (9). These drugs potentiated the cataleptic effect of neuroleptics. On the other hand cyclo-oxygenase inhibitors, paracetamol and indomethacin significantly reduced the descent latency time. The mechanism whereby PG synthesis stimulators potentiate, while PG synthesis inhibitors antagonise, neuroleptic-induced catalepsy can be explained as follows: Normally, following the blockade of the

postsynaptic DA receptors by neuroleptics, there is a compensatory "feedback" increase of DA neuronal activity with resultant increase in DA release which counteracts to some extent the neuroleptic-induced blockade of DA receptors (1). We hypothesize that PG synthesis stimulators, by increasing PGE<sub>1</sub> levels, inhibit DA neuronal activity and make less DA available for release and to compete with neuroleptic for the postsynaptic DA receptor sites with resultant potentiation of neuroleptic-induced catalepsy. In contrast, PG synthesis inhibitors by decreasing PGE<sub>1</sub> levels remove the inhibitory influence of PGE<sub>1</sub> on DA neuronal activity thereby making more DA available for release and to compete with the neuroleptic for the postsynaptic DA receptor sites with resultant antagonism of neuroleptic-induced catalepsy. Recently a decrease in metoclopramide induced catalepsy after pretreatment with paracetamol (50 mg/kg, ip) and indomethacin (25 mg/kg, ip) has been reported (2). However, in the present study such high doses of these blockers were less effective in antagonising the cataleptic effect; the possible explanation could be more selective inhibition of cyclo-oxygenase enzyme involved in the synthesis of PGE<sub>2</sub> series at these dose levels and thereby causing a relative increase in PGE<sub>1</sub> levels and catalepsy. Thus in conclusion, we suggest that prostaglandins by modulating the DAergic neuronal activity can influence neuroleptic induced catalepsy.

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