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DIFFERENTIAL EFFECTS OF SEROTONIN ANTAGONISTS ON

HYPOTHERMIA AND STEREOTYPED BEHAVIOR INDUCED BY

APOMORPHINE AND LERGOTRILE IN RATS

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University of the Pacific, 1978

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This thesis, written and submitted by

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Introduction

The naturally occuring ergot alkaloids of the fungus, __Claviceps__ __purpurea__, and their many derivatives have been of neuropharmacological interest for many years because of their ability to affect peripheral and central adrenergic and serotonergic systems. More recently, selected compounds such as lergotrile (2-chloro-6-methyl ergoline-8-__beta__-acetonitrile) and bromocryptine (2-bromo-__alpha__-ergocryptine), have been given additional attention due to their possible therapeutic potential in the treatment of parkinson's disease, acromegaly and other disorders. There have been considerable data published attempting to establish the mechanism(s) whereby the ergot compounds exert their effects. A large portion of these experiments involves the interaction of ergot compounds with dopaminergic systems. This is a logical course of study, since many of the actions of the ergot compounds mimic the actions of compounds known to affect dopaminergic neurons, __e.g.__ antagonists such as the

phenothiazines and butyrophenones, and agonists such as levodopa and apomorphine. In the last decade, much attention also has been focused on the role of serotonin (5-hydroxytryptamine) in the mediation of dopaminergic systems. There have been many conflicting reports published as to the role of serotonin but it is still uncertain whether or not serotonin does indeed play a role. The present study investigates two dopaminergic effects of the standard dopamine agonist apomorphine and the ergoline lergotrile and the similarities or differences that exist when serotonergic function is altered.

Literature Survey

1. Hypothermic action of apomorphine

An effect of apomorphine on rodent thermoregulatory function was first described by Lapin and Samsonova (1968a, 1968b). The first convincing evidence that linked drugs which stimulate dopamine receptors with a decrease in core temperature in rats and mice was presented in 1972 (Kruk, 1972; Fuxe and Sjoqvist, 1972). Since that time, apomorphine has been consistently reported to cause a dose-related hypothermia in rats and mice using a variety of injection techniques (Barnett et al., 1972; Chiel et al., 1974; Ary et al., 1977; Cox and Lee, 1978). Kruk (1972) found that dopamine, amphetamine and apomorphine injected intracerebroventricularly into rats, caused a fall in core temperature accompanied by a rise in skin temperature. A maximum drop of about one degree centigrade was observed with all three

drugs, this effect being completely antagonized by the specific dopamine antagonist pimozide. Fuxe and Sjoqvist (1972) obtained a drop of 3° to 4° C in the body temperature of mice administered apomorphine by intraperitoneal inject- ion, and this effect was blocked by a dose of haloperidol that had no effect on body temperature itself. The nor- adrenaline antagonist phenoxybenzamine and the anticholiner- gic agent atropine failed to block the hypothermic action of apomorphine, thereby precluding alpha adrenergic or muscarinic cholinergic mechanisms of action for apomorphine. These observations suggest that the hypothermic action of apomorphine is exclusively mediated by dopamine receptors.

The apparent mechanism of action of apomorphine at the dopamine receptor had been determined several years earlier by Ernst (1967) and Anden (1967). Apomorphine-induced effects were found to be independent of exogenous catechol- amine release, which is contrary to the action of amphet- amine, which produced its action through the release of endogenous catecholamines. It was concluded that the action of apomorphine was that of a direct agonistic action on the receptor structure. Thus it appears that apomorphine induces hypothermia by a direct stimulation of dopamine receptors.

It has long been recognized that the preoptic anterior hypothalamus has an important thermoregulatory function in warm-blooded animals (Reid et al., 1968). Utilizing central microinjection techniques, it has been determined that the

site of action of apomorphine (Cox and Lee, 1978) and
dopamine (Quock and Gale, 1974) is a well defined area of
dopamine receptors in the preoptic anterior hypothalamus.
This area was found to be sensitive to the antagonistic
action of haloperidol in both studies.

Tolerance to the hypothermic action of apomorphine has
been demonstrated. Daily intraperitoneal injections of
apomorphine have been reported to decrease the hypothermic
response of subsequent injections of apomorphine and other
dopamine agonists (Chiel et al., 1974). It was suggested
that tolerance to the hypothermic effects was due at least
in part to a decrease in sensitivity of the dopamine recep-
tors involved. Tolerance to the hypothermic action of apo-
morphine has also been demonstrated to occur after chronic
rostral hypothalamic injections (Ary et al., 1977), but
repeated injections into the lateral ventricle fail to pro-
duce tolerance. Therefore, the possibility of two different
types of dopamine receptors at two different sites has been
suggested -- those surrounding the lateral ventricles being
resistant to tolerance.

2. Apomorphine-Induced Stereotypic Behavior

It has been known for over one hundred years that apo-
morphine, administered by a variety of routes, produces a
behavioral syndrome in rats consisting of continuous, pur-
poseless, compulsive actions (Harnack, 1874). At threshold
doses, an increase in exploratory activity coupled with dis-
continuous sniffing is manifested. With increased dosage,

normal activities such as grooming and feeding are extin-
guished and replaced with continuous sniffing, accompanied
by small, repetitive head movements. High doses of apomor-
phine elicit a continuous gnawing, biting and licking
response and the rat restricts its locomotion to a very
small area. The nature of this behavior justifies the term
"stereotypy," which has been applied to it (DiChiara and
Gessa, 1978). Stereotypy has been described in many species
including rodents, cats, dogs, rabbits, pigeons and others
(Randrup and Munkvad, 1967; DiChiara and Gessa, 1978).

Such stereotyped behavior in rodents can be quantified
according to the dose-related appearance of one or more of
the behavioral components (Ernst, 1967; Costall and Naylor,
1972). Such scoring scales rate smiffing behavior (with
locomotion) lowest while rating continuous gnawing (with
little or no locomotion) the highest. Details of one such
scoring system are shown in Table I. The appearance of the
sniffing at low doses and gnawing at higher doses appears to
be directly correlated with the appearance of apomorphine
in brain tissue following peripheral injection (Butterworth
and Barbeau, 1975). Other scoring systems exist for apomor-
phine-induced stereotypy, e.g. "gnaw compulsion" syndrome
was considered to be present (Ernst, 1969) when rats gnaw
at the wire mesh on the bottom of the cage for at least half
a minute and, when loosened from the wire, start gnawing
again. Others have used a quantal approach to determine the
presence of stereotyped behavior (Goetz and Klawans, 1974;

Table I -- Stereotyped behavior rating scale used in
the present study

---

0 = Rats exhibiting no stereotyped behavior; behavior
is indistinguishable from that of control animals.

1 = Rats exhibiting periodic sniffing and repetitive
head and limb movements.

2 = Rats exhibiting continuous sniffing and repetitive
head and limb movements; exploratory activity is
also present.

3 = Rats exhibiting occasional licking, biting or
gnawing; exploratory activity is also present.

4 = Rats exhibiting persistent and intense licking,
biting or gnawing; locomotion is restricted to
a small area.

5 = Rats exhibiting persistent and intense licking,
biting or gnawing restricted to one location.

Jacobs, 1974). It has been observed that the presence of wooden shavings on the cage floor facilitates the gnawing component of stereotypy produced by intermediate doses of apomorphine, and that distracting stimuli, such as loud noise, inhibit this phenomenon (DiChiara and Gessa, 1978).

Ernst (1967) concluded that apomorphine produces stereotyped behavior in rats by direct stimulation of the dopamine receptors located in the neostriatum. This hypothesis is supported by several other studies that have been reported. In the next three paragraphs these studies will be discussed.

The ability of apomorphine to induce stereotyped behavior has been shown to be abolished by lesions of the corpus striatum (Amsler, 1923; Wolfarth et al., 1973). By stereotaxically implanting crystalline apomorphine or L-dopa into the brain of rats, Ernst and Smelik (1966) discovered that areas producing stereotyped behavior were the dorsal part of the caudate nucleus and the globus pallidum. No stereotyped behavior was produced by implants into the ventral part of the caudate nucleus, in the region medial to the caudate nucleus (nucleus lateralis septi), in subthalamic structures, or in the substantia nigra.

As noted earlier, evidence for the direct action of apomorphine on dopamine receptors was presented by Ernst (1967) and Anden (1967). L-dopa, apomorphine and amphetamine all produce similar stereotyped behavior in rats. Depletion of brain amines by alpha-methyldopa failed to block apomorphine-induced stereotypy but profoundly antagon-

ized amphetamine-induced stereotypy. Alpha-methyltyro-
sine and reserpine produce the same results. Fog (1967)
demonstrated that intracerebral microinjections of dopamine
into the corpus striatum restore amphetamine-induced stereo-
typy that has been inhibited by alpha-methyltyrosine. This
strongly suggests that apomorphine does not act by dopamine
release, but has a dopamine-like effect on the receptor
structure. Amphetamine would appear to act via the release
of endogenous amines. Further evidence of this is the ob-
servation that monamine oxidase inhibitors can potentiate
the behavioral effects of amphetamine (Ernst, 1967) and L-
dopa but exert no effect on apomorphine-induced stereotyped
behavior. Apomorphine does have structural similarities to
dopa, and it has been suggested that the presence of hydroxyl
groups at the para- and meta- positions of the phenol ring
in the phenol-ethylamine configuration is obligatory for a
direct action on gnawing behavior (Ernst, 1967). Apomorphine
possesses this catechol configuration; amphetamine does not
(Fig. 1).

Further support for the dopaminergic nature of apomor-
phine is that among neuroleptics, the most powerful antagon-
ists of apomorphine are haloperidol, spiroperidol and pimo-
zide. These compounds are reported to be pure dopamine
receptor blockers at doses effective in antagonizing apomor-
phine-induced stereotyped behavior (DiChiara and Gessa, 1978).

In contrast to the above widely accepted theories on
apomorphine action, it has been shown that lesions of
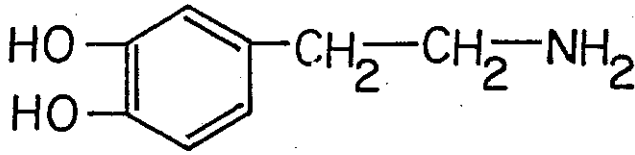
DOPAMINE
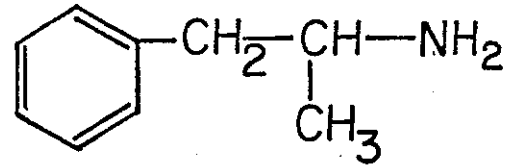
AMPHETAMINE
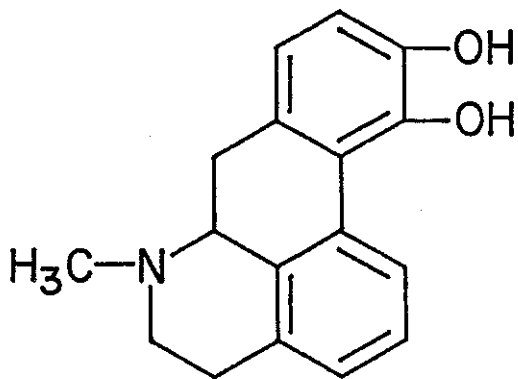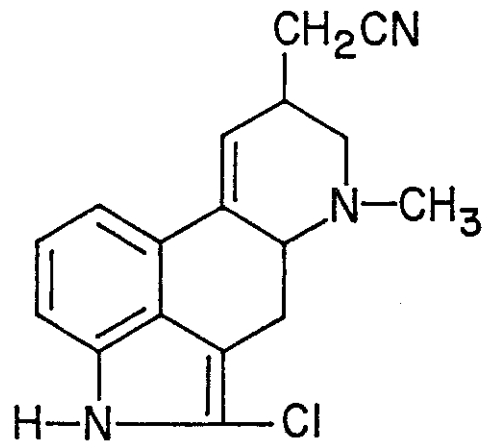
APOMORPHINE

LERGOTRILE

Figure 1 -- The structural relationships between dopamine, amphetamine, apomorphine and lergotrile.

dopaminergic tracts or nerve cells are effective in abolishing or decreasing apomorphine-induced stereotypy (Costall and Naylor, 1972). This would indicate that apomorphine-induced stereotypy requires the presence of intact dopaminergic terminals, and that apomorphine produces stereotypy via some presynaptic mechanism. Further evidence indicating a presynaptic action for apomorphine is that disruption of intraneuronal amine stores by oxypertine and RO-04-1284 (catecholamine depletors) has been shown to reduce or abolish the stereotypic effects of apomorphine (Costall and Naylor, 1973a). The electrolytic lesion techniques employed by Costall and Naylor (1972, 1973b) have come under criticism recently by DiChiara and Gessa (1978). Their studies are in disagreement with data obtained by specific chemolytic destruction of dopamine terminals with 6-hydroxydopamine (Schoenfeld and Uretsky, 1972). Reasons suggested for this descrepancy include the incompleteness of the electrolytic lesions or interference with other non-dopaminergic nerve tracts necessary for the expression of apomorphine-induced stereotypy.

Further evidence for the presynaptic activity of apomorphine, but not intrinsically linked to stereotypy, is the ability of apomorphine to inhibit tyrosine hydroxylase, the enzyme responsible for converting tyrosine to dopa (Goldstein et al., 1970). It has been proposed that a negative feedback mechanism exists in dopaminergic neurons, and that the stimulation of dopamine terminals by apomorphine activates

this mechanism (Kehr et al., 1972). Studies determining
the rate of disappearance of dopamine after tyrosine hydroxy-
lase inhibition with alpha-methyltyrosine have shown that
apomorphine consistently causes a decrease in the rate of
disappearance of dopamine (Anden et al., 1967; Butcher and
Anden, 1969). Goldstein and colleagues (1970) found that
apomorphine inhibited tyrosine hydroxylase as well as the
~~synthesis of dopamine from tyrosine in striatal slices. The~~
addition of haloperidol to the preparation did not affect
the inhibitory effect of apomorphine. This experiment
indicates that the inhibitory effectiveness of apomorphine
on striatal slices is not due to stimulation of dopamine
receptors, but due to a direct action on tyrosine hydroxy-
lase. The catechol structure of apomorphine supports this
theory.

Costall and Naylor (1975) have attempted to differen-
tiate pharmacologically and anatomically two components of
stereotyped behavior, a low-intensity component (sniffing
and repetitive movements) and a high-intensity component
(gnawing). As mentioned earlier, low doses of apomorphine
cause sniffing and repetitive head and limb movements, where-
as high doses elicit intensive gnawing. Intracerebral
application of dopamine to the tuberculum olfactorium and
nucleus accumbens septi produces sniffing and movements
characteristic of the low-intensity component. Lesions of
these areas were effective in reducing the stereotyped
sniffing and head and limb movements induced by apomorphine.

The substantia nigra and nucleus amygdaloideus centralis were determined to be the effectors for the high-intensity component using the same intracerebral application and lesion techniques. It has become apparent from these findings that other brain structures and pathways are also important in the expression of the stereotypic effects of apomorphine besides those of the neostriatum (Ernst and Smelik, 1966). Paleostriatal structures (nucleus pallidus) and mesolimbic areas (tuberculum olfactorium, nucleus amygdaloideus centralis and lateralis, nucleus accumbens septi) as well as those of the neostriatum (caudate nucleus and putamen) all appear to have important functions in the full expression of apomorphine-induced stereotypic behavior.

3. The Role of Serotonin in Thermal Regulation and Stereotypy

There exists considerable evidence that serotonin plays a role in many central nervous system functions such as temperature regulation, neuroendocrine regulation, sleep, extrapyramidal function and behavior (Chase and Murphy, 1973). Recently it has been postulated that serotonin may have a function in regulating or mediating the central effects of dopaminomimetics such as apomorphine. Conflicting reports preclude the formulation of a single theory to explain the role that serotonin may play in these systems

Attempts to evaluate the role serotonin may play in the central nervous system or in the action of dopamine agonists may be grouped into four approaches. The first approach is biochemical, whereby attempts are made to increase or

decrease brain serotonin. Systemically administered pre-
cursors of serotonin (L-tryptophan and 5-hydroxytryptophan)
are believed to increase brain serotonin and neural trans-
mission, but evidence exists that this method may also inter-
fere with other catecholamines (Chase and Murphy, 1973).
The opposite approach is to administer a drug that is
believed to decrease brain serotonin and neural transmission.
~~Parachlorophenylalanine is an inhibitor of tryptophan~~
hydroxylase and leads to a profound depletion of brain sero-
tonin (Koe and Weissman, 1966). However, it has been shown
that parachlorophenylalanine also lowers the levels of
other brain amines including norepinephrine and dopamine
(Tagliamonte et al., 1973).

A pharmacologic approach is to use selective blocking
agents for serotonin receptors in the brain. Drugs such as
cyproheptadine, cinanserin and methysergide are believed to
block serotonin receptors directly. The major difficulty
with these pharmacologically based investigations is
finding a drug that acts exclusively on serotonin neurons.

Physical techniques have been utilized for the in vitro
study of serotonin function. Lesions of the midbrain raphe
are reported to deplete markedly the serotonin concentration
of forebrain (Kostowski et al., 1968), whereas electrical
stimulation of this area accelerates the synthesis and
release of serotonin (Kostowski et al., 1969). As with
pharmacological techniques, physical intervention is some-
what nonspecific and may affect non-serotonergic nerve

fibers that traverse the raphe nucleus (Chase and Murphy, 1973).

The fourth major approach to the study of serotonin mechanisms involves histofluorescent techniques. By measuring the brain levels of serotonin or 5-hydroxyindoleacetic acid, its principal deaminated metabolite, the steady state or turnover rate of serotonin can be monitored, and the relative activation of serotonin neurons can be estimated (Tozer et al., 1966).

It has been reported that apomorphine increases serotonin turnover (Scheel-Kruger and Hasselager, 1974; Grabowska, 1975; Maj, 1975). Apomorphine has been found to accelerate the disappearance of 5-hydroxyindoleacetic acid from the brain of pargyline-pretreated (a MAO inhibitor) rats as well as to facilitate the depletion of brain serotonin caused by synthesis inhibition (Grabowska, 1975). Depletion of brain serotonin was abolished when rats were treated with the dopamine antagonist, spiroperidol. Apomorphine has been reported to increase brain serotonin and 5-hydroxyindoleacetic acid levels, accelerate the disappearance rate of serotonin after synthesis inhibition with alpha-propyldopacetamide, and intensify serotonin fluorescence in raphe nuclei (Maj, 1975). Dopamine blockers (spiroperidol and pimozide) counteract these effects of apomorphine, and this has led to the suggestion that these agents influence serotonin neurons through a secondary mechanism, with the primary effects being directed at dopamine

receptors. Further experiments have supported this theory. Apomorphine will increase the concentration of serotonin and 5-hydroxyindoleacetic acid in the raphe region in the mesencephalon of normal rats but not in rats with a mesencephalic-diencephalic transection (Grabowska et al., 1976). This transection interrupts the descending pathway originating from dopamine structures of the forebrain. Transection alone was reported to cause no change in raphe serotonin or 5-hydroxyindoleacetic acid. Therefore, it appears that apomorphine can activate serotonin neurons indirectly. This activation of serotonergic neurons may be important in the mediation of some of the pharmacological effects of apomorphine and other dopaminomimetics.

Serotonin appears to also have a critical role in the complex network of neural factors which regulate body temperature. Brain serotonin has been shown to increase in the rat during heat stress (Reid et al., 1968) and it has been proposed that central serotonin pathways may be involved in the response to heat stress in the rat.

Several studies indicate that apomorphine-induced thermal effects have a serotonin link. Midbrain raphe lesions have been shown to attenuate the hypothermic effects of apomorphine in rats (Grabowska et al., 1974). Selective chemolytic destruction of serotonin neurons with 5,6-dihydroxytryptamine, as well as serotonin depletion with para-chlorophenylalanine, has been reported to strongly inhibit

the hyperthermia induced by apomorphine and other dopamine agonists in rabbits (Carruba et al., 1978). Intrahypothalamic pretreatment with cyproheptadine or methysergide has been shown to block the hypothermic effect of dopamine agonists (Cox and Lee, 1979). LSD (lysergic acid diethylamide) will inhibit apomorphine-induced hypothermia and this effect is believed to be due to stabilization of serotonin within the receptor (Grabowska et al., 1973). Thus, strong evidence indicates that apomorphine and other dopaminomimetics may mediate thermal effects in mammals through a serotonergic link.

While there is general agreement on a serotonergic link in apomorphine-induced hypothermia, apomorphine-induced stereotypy does not enjoy such agreement. Studies have shown that an increase in brain serotonin induced by 5-hydroxytryptophan or l-tryptophan or a reduction in brain serotonin with parachlorophenylalanine has no effect on apomorphine-induced stereotypy (Rotrosen et al., 1972; Baldessarini et al., 1975). The serotonin lesioning agents 5,6- or 5,7-dihydroxytryptamine (Baldessarini et al., 1975) and the serotonin antagonist methysergide (Rotrosen et al., 1972) have also been reported to have no effect on apomorphine-induced stereotypy.

Certain reports indicate that a decrease in serotonin concentration or a blockade of serotonin receptors can potentiate apomorphine-induced stereotypy (Weiner et al., 1975; Molgilnicka et al., 1977). Treatments found to potentiate

apomorphine-induced stereotypy included parachlorophenyl-alanine, cyproheptadine, methysergide and methergoline. The administration of 5-hydroxytryptophan was found to inhibit apomorphine-induced stereotypy (Weiner et al.,1975). Consequently, it has been suggested that serotonin plays an antagonistic role to that of dopamine in stereotyped behavior (Molgilnicka et al., 1977). In agreement with this, ~~methamphetamine-induced stereotypy has been found to be~~ inhibited by l-tryptophan treatment and potentiated by parachlorophenylalanine treatment (Balsara et al., 1979).

In direct contrast to these findings, the serotonin agonist quipazine and the serotonin reuptake blocker ORG 6582 have been reported to convert apomorphine-induced low-intensity sniffing to high-intensity gnawing (Carter and Pycock, 1978), and cyproheptadine and metergoline have been reported to reduce apomorphine-induced stereotypy. In addition, parachlorophenylalanine, cinanserin and methysergide treatments have been reported to block l-dopa- or l-trypto-phan-induced lateral head weaving and reciprocal forpaw treading in rats (Jacobs, 1974). Dopamine synthesis inhibition with alpha-methyltyrosine or receptor blockade with pimozide apparently had no effect on the stereotypy in these studies. Therefore, the role that serotonin may play in apomorphine-induced stereotyped behavior remains very unclear.

4. Pharmacology of Lergotrile and Related Ergot Compounds

The naturally occuring ergot alkaloids and the hundreds

of chemically related semisynthetic agents that are now
available have been described as a treasure chest of pharma-
cologically active and clinically useful compounds
(Saameli, 1976). Crude extracts of the parasitic fungus
Claviceps purpurea have been used for centuries as an
oxytocic, but the cornerstone of the pharmacology of ergot
is the classic work done by Sir Henry Dale early in the
twentieth century. His demonstration of adrenaline rever-
sal using ergot extracts in a spinal cat has been the basis
for many studies in receptor pharmacology (for a review
see Schild, 1976).

The influence of ergot compounds on noradrenergic
synapses has been well studied. Dihydrogenated ergot alka-
loids and ergotamine have been demonstrated to have direct
venoconstrictor activity (Mellander and Nordenfelt, 1976).
Aellig (1976) and Chu and colleagues (1976) have attributed
part of this venoconstrictor activity to alpha-adrenoceptor
stimulation. Other noradrenergic effects of ergot compounds
have been demonstrated such as presynaptic noradrenaline
release and the blockade of alpha-adrenoceptors (Salzmann
and Pacha, 1976). Inhibition of catecholamine reuptake has
been demonstrated with dihydroergotoxine in central nervous
tissue (Meier-Ruge and Iwangoff, 1976).

Recently, much attention has focused on the dopamin-
ergic activity of ergot compounds, probably due to the
clinical application of ergot compounds in the treatment
of such pathologies as parkinsonism, acromegaly, hyper-

prolactinemia-hypogonadism and puerperal lactation. The
course of study on the dopaminergic agonist and antagonist
activities of ergot derivatives and lergotrile have been
explored in two different ways: (i) those which have employ-
ed biochemical and endocrinological techniques, and (ii)
those which have used these compounds clinically as replace-
ments for traditional dopaminergic agents.

Several studies have demonstrated the interaction of
ergot derivatives and lergotrile with the dopamine receptor.
After pretreatment with alpha-methyltyrosine, histochemical
studies on neostriatal and limbic dopamine nerve terminals
revealed a dose-dependent deceleration of dopamine fluor-
escence in rats treated with ergocornine or bromocryptine
(Corrodi et al., 1973). Lergotrile has also been reported
to slow the decline in dopamine concentration after synthesis
inhibition with alpha-methyltyrosine along with being able
to lower whole brain DOPAC (3,4-dihydroyxphenylacetic acid)
concentration in rats (Fuller and Perry, 1978). Lergotrile
has been shown to cause a dose-dependant and haloperidol-
reversible depression of dopamine cell-firing rates in the
pars compacta of the rat substantia nigra (Walters et al.,
1979). All of these observations are consistent with the
theory that ergolines and lergotrile can act as direct
dopamine agonists in vivo.

In vitro studies indicate that bromocryptine and ler-
gotrile have mixed putative agonist-antagonist activity on

dopamine receptors. Receptor binding studies have shown
that lergotrile has a higher affinity for radiolabeled
dopamine binding than bromocryptine, while bromocryptine has
a higher affinity than lergotrile for radiolabeled haloper-
idol binding sites (Lew et al., 1977). Lergotrile has also
been shown to antagonize the dopamine-stimulated adenyl
cyclase activity in the striatum (Kebabian et al.,1977).
In light of these results, it has been suggested that
several categories of pharmacologically distinct dopamine
receptors exist (Kebabian and Kebabian, 1978) and that ler-
gotrile possesses varying degrees of agonist-antagonist
properties with respect to these various receptors.

The role of hypothalamic dopamine in inhibiting pitui-
tary prolactin release provides a very good opportunity for
studying the dopaminergic activity of a variety of compounds.
Neuroleptics of many classes (butyrophenones, phenothiazines,
thioxanthines) increase prolactin secretion in man in a
dose-dependent manner without affecting plasma levels of
other pituitary hormones (Langer and Sachar, 1977). This
response to neuroleptics is attributed to the blockade of
dopamine in the hypothalamic-pituitary axis, as dopamine
completely antagonizes the response to the neuroleptics
when administered. Lergotrile has been shown to inhibit
prolactin secretion in man and to attenuate the perphenazine-
induced secretion of prolactin (Lemberger et al., 1974).
This effect was very specific; no significant changes in
the other pituitary hormones measured (GH, T_3, T_4, LH, FSH)

were observed. Many ergoline derivatives have been shown to have the same effect (Clemens et al., 1974). The mechanism of action for lergotrile in prolactin secretion inhibition has been suggested to be due to an activation of adeno-hypophyseal dopamine receptors (Clemens et al., 1975). A major metabolite of lergotrile in humans, 13-hydroxy-lergo-trile, has has been demonstrated to be a potent inhibitor of prolactin secretion (Parli et al., 1978).

Lergotrile has been shown to raise the levels of serum growth hormone in normal humans, but to lower the hormone in acromegalic patients (Kleinberg et al., 1978; Thorner et al., 1978). Thorner and coworkers (1978) have demonstrated the dopaminergic nature of this action by attenuating the response to lergotrile with metoclopramide, a dopamine antagonist. Bromocryptine has also been demonstrated to lower serum growth hormone in patients with acromegaly (Thorner and Besser, 1976). Both lergotrile and bromocryptine show promise in the treatment of acromegaly. Clinical improvement is seen as a decrease in sweating, thinning of extremities, improvement in glucose tolerance and, of course, decrease in serum growth hormone levels.

Both lergotrile and bromocryptine have been used successfully in the treatment of parkinsonism (Lieberman et al., 1975; Goldstein et al., 1978; Klawans et al., 1978). Binding studies to striatal membranes have demonstrated that the efficacy of these compounds in the treatment of parkinsonism can be attributed to the direct stimulation of dopamine

receptors (Goldstein et al., 1978). One particularly
interesting observation in all of these studies is that
lergotrile and bromocryptine were effective in patients
who were no longer responsive to L-dopa and carbidopa
therapy.

Certain ergot derivatives have been demonstrated to
induce stereotypy and/or hypothermia in rodents. Lisuride
hydrogen maleate has been shown to produce dose-dependent
stereotypy and hypothermia in mice (Horowski and Wachtel,
1976). Stereotypy was induced in control as well as
reserpinized mice, indicating a direct dopaminergic action
for this ergot derivative. A dose-response relationship
has also been demonstrated for bromocryptine-induced hypo-
thermia in rats (Calne and Claveria, 1975). It was suggest-
ed that the hypothermia produced was the result of bromo-
cryptine stimulating dopamine receptors in brain areas con-
trolling body temperature.

Statement of the Problem

Apomorphine and lergotrile induce hypothermia and
stereotypy in the rat. It is generally accepted that these
effects are due to stimulation of dopamine receptors, as
both effects can be completely antagonized by haloperidol
or pimozide. Several studies have indicated that such
central actions of dopaminomimetics may be affected by sero-
tonergic mechanisms.

Apomorphine-induced hypothermia in rats appears to be
mediated via a serotonin link (Grabowska et al.,1973;

Grabowska, 1974; Cox and Lee, 1979). One study has in-
dicated that such a serotonin link may mediate apomorphine-
induced hyperthermia in rabbits (Quock and Horita, 1974).
While there are many studies examining the role of serotonin
in apomorphine-induced temperature effects, there are very
few studies that have examined the role of serotonin in
the temperature effects induced by ergot derivatives. One
~~study used bromocryptine to induce hyperthermia in rabbits,~~
and found this effect to be antagonized by treatment with
either parachlorophenylalanine or 5,6-dihydroxytryptamine
(Carruba et al., 1978). The role that serotonin may play
in lergotrile-induced hypothermia has not been studied.

The role that serotonin may play in apomorphine-
induced stereotypy is very unclear. This may be due in part
to the difference in methods used to evaluate the behavior
and in part to the absence of a specific agonist or antagon-
ist of serotonin, a problem that plagues many serotonin
studies. Each of the biochemical, pharmacologic and physical
techniques used to facilitate or interrupt serotonergic
activity may affect non-serotonergic nerve activity as well
(Chase and Murphy, 1973).

Since both apomorphine and lergotrile produce similar
effects which have been attributed to dopaminergic activity,
the possibility exists that both compounds have a similar
mechanism of action. If this is true, it would be expected
that any serotonergic influence on the effects of either drug
would be the same. The present study was undertaken to compare

two effects induced by apomorphine (hypothermia and stereotypy) with the corresponding effects induced by lergotrile and the changes that may arise in these responses when serotonin function is altered. The results of this study should provide some evidence as to whether apomorphine and lergotrile produce their effects through a common or parallel dopaminergic mechanism.

Materials and Methods

1. Animals

Male Wistar rats (Simonsen Laboratories, Gilroy, California), weighing between 150-250 g, were housed prior to experimentation in community cages on a standard light-dark schedule (light: 0700-1400) and given food (S/L Custom Lab Diet-G4.5, Simonsen Labs) and water ad libitum. Ambient temperature was regulated at $22^\circ \pm 1^\circ$ C. For each experiment, naive animals were chosen at random, weighed and placed in individual cages. Food and water were withheld during the course of each experiment.

2. Drugs

Apomorphine hydrochloride (APO, Merck and Co.), lergotrile mesylate (LER, Eli Lilly), cyproheptadine hydrochloride (CYP, Merck, Sharp and Dohme), cinanserin hydrochloride (CIN, Squibb and Sons), and parachlorophenylalanine methyl ester hydrochloride (PCPA, Sigma) were all

prepared as aqueous solutions immediately prior to use using duoble-distilled water. Haloperidol (HAL, McNeil) was supplied in prepared Haldol[R] injection ampules and was diluted to final concentration with double-distilled water.

3. Procedure

All experiments were started at 0900 with drug and control pretreatments given by 1100. Double-distilled water served for control injections. All injections were given intraperitoneally with pretreatment and challenge injections given on opposite sides of the peritoneal cavity. A constant injection volume of 1.0 ml/kg was used except for PCPA and its control, which were given at 2.0 ml/kg. All pretreatments were given 30 minutes prior to the challenge injections except for PCPA and its control, which were given 48 hours prior to challenge injections of APO or LER. All doses given refer to the salt of the compound except for HAL, where doses were given as the free base. The significance of the drug effects were evaluated using the Student't t test. Analysis of variance between the base-line body temperatures was evaluated using Dunnett't t test.

4. Measurement of Body Temperature

During experimentation, the animals were housed individually in metal cages (24 x 30 x 15 cm) on absorbant bedding in a controlled temperature room ($22^\circ \pm 1^\circ$ C) after being weighed. The animals were allowed to acclimatize for 60 minutes prior to any temperature recording. An electron-

ic telethermometer with a flexible rectal probe (Yellow Springs Instruments #43TA, probe #402) was used for all temperature measurements, and was inserted 5.0 cm past the rectum (insertion duration = 30 seconds). Baseline temperatures were taken every 15 minutes for at least one hour prior to any injection. Recordings were made 15 and 30 minutes after pretreatment injections to assure that there had been no variation from the baseline temperature. For APO experiments, recordings were made every 15 minutes for 90 minutes, and for LER, every 30 minutes for 300 minutes -- this difference reflects the duration of action of each drug on body temperature. The change in body temperature was determined by subtracting each interval's reading from the baseline temperature for each animal.

5. Measurement of Stereotypy

The animals were housed in clear plexiglass cages (25 x 45 x 15 cm) in a silent, evenly lit room for 60 minutes prior to the experiment. The floor of the cages was filled with 1-2 cm of absorbant bedding (KC Pharmacal) upon which the animals could gnaw or bite. This material was found to be very satisfactory to observe the gnawing/biting component of stereotypy. Opaque screens were placed between individual cages to prevent behavioral interaction between animals. In all experiments, the animals were injected at staggered intervals of 2 minutes, and the intensity of stereotypy was assessed using a modified version (Table I) of the scale developed by Costall and

Naylor (1972). A total stereotypy score was assigned to each animal consisting of the total of the 18 scores (taken every 5 minutes over the 90-minute observation period), although very often the duration of stereotypy was considerably less than 90 minutes.

6. Determination of Brain Serotonin Content

Determination of whole brain serotonin content was made by spectrofluorimetric assay by the method of Lai and coworkers (1978). Rats were killed by rapid decapitation 48 hours after the double-distilled water or PCPA injections. The entire brain was quickly removed, washed with ice cold 0.9 percent saline, weighed and homogenized for 4.0 seconds (Brinkmann PCU-2 Polytron) in two volumes of cold 0.3 N perchloric acid. The homogenate was centrifuged at 2000 $\underline{x}$ g for 10 minutes. Eight hundred μl of the supernate was added to 2.0 ml Na_2HPO_4 buffer containing 0.1 M DEHPA (diethylhexyphosphoric acid) in 1.2 ml $CHCl_3$. After shaking for two minutes, the organic layer was separated from the aqueous layer by centrifugation (600 $\underline{x}$ g for 5 minutes). One ml of the organic layer was removed and added to a test tube containing 2.0 ml heptane and 0.6 ml 0.2 N HCl and shaken for two minutes. Again the organic layer was separated from the aqueous layer by centrifugation (600 $\underline{x}$ g for 5 minutes). Two hundred μl of the aqueous layer was transferred to a test tube to which was added 100 μl $\underline{o}$-phthalaldehyde reagent (50 mg percent in methanol). This mixture was

vortexed immediately. Eight hundred μl concentrated HCl (12 N) was then added and vortexed immediately. The resulting mixture was heated in an 85° C water bath for 30 minutes, then cooled to room temperature (22° C) in a water bath. The serotonin phosphor was read at an activation wavelength of 356 nm and a fluorescence wavelength of 480 nm. Serotonin creatinine sulfate (50 μg/ml in 0.1 N HCL) was used as a standard.

Results

1. Hypothermia

Apomorphine and lergotrile produced a dose-related
hypothermia when injected intraperitoneally into rats (Fig.
2,3). Pretreatment with haloperidol 0.5 mg/kg very highly
significantly antagonized the maximum drop in body temper-
ature for both doses of apomorphine (Fig. 4,5) and all
three doses of lergotrile (Fig. 6,7,8) without significantly
affecting body temperature alone (Fig. 9). Pretreatment
with cyproheptadine HCl 0.5 mg/kg had no significant effect
on apomorphine-induced hypothermia (Fig. 4,5) but signifi-
cantly potentiated the hypothermic response of lergotrile
(Fig. 6,7,8). Cyproheptadine HCl 0.5 mg/kg had no sig-
nificant effect on body temperature itself (Fig. 9). Pre-
treatment with cinanserin HCl 5.0 mg/kg very highly signifi-
cantly attenuated apomorphine-induced hypothermia (Fig. 10)
while very highly significantly potentiating the hypothermic
response of lergotrile (Fig. 11).

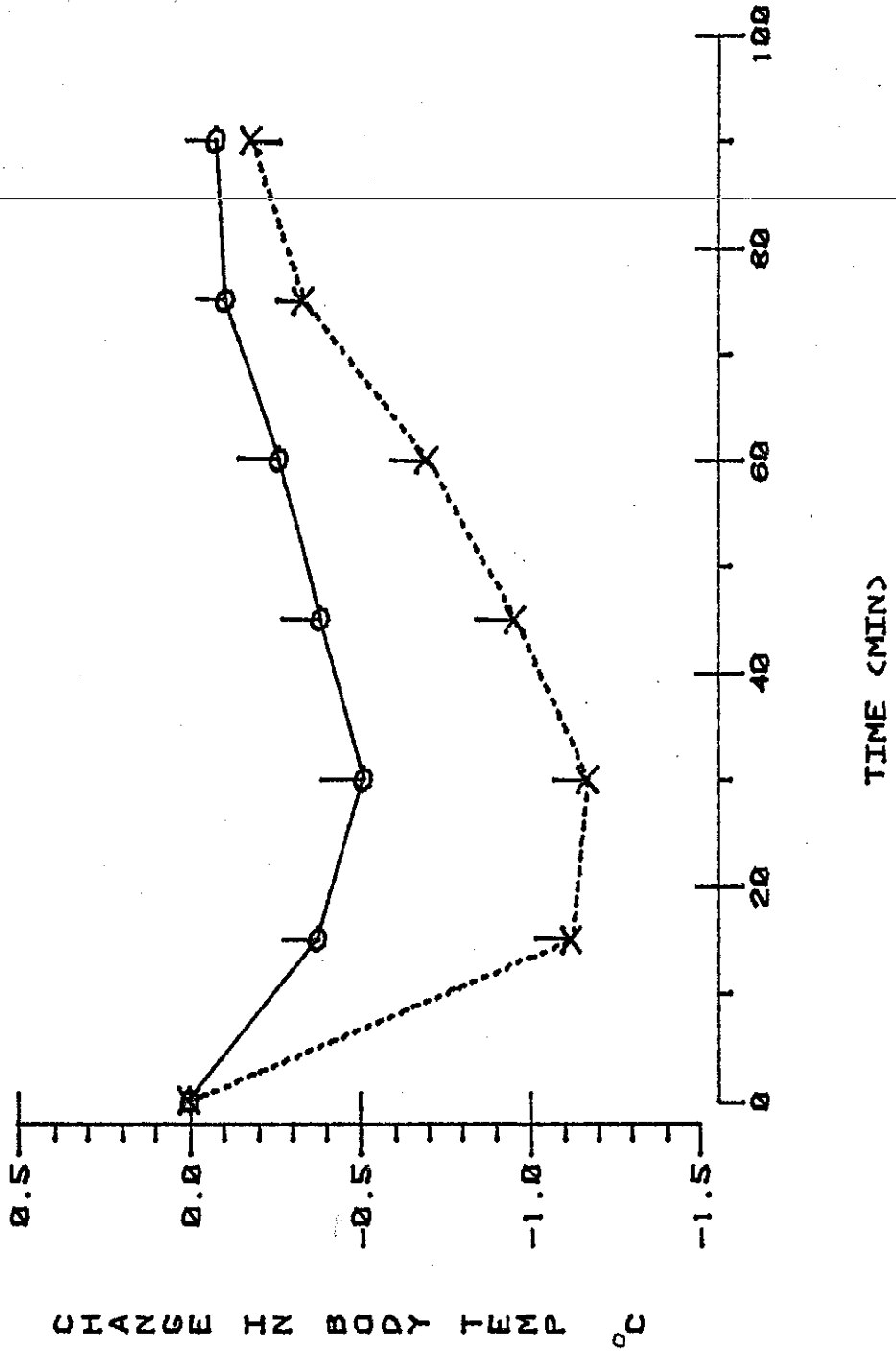A single injection of parachlorophenylalanine methyl
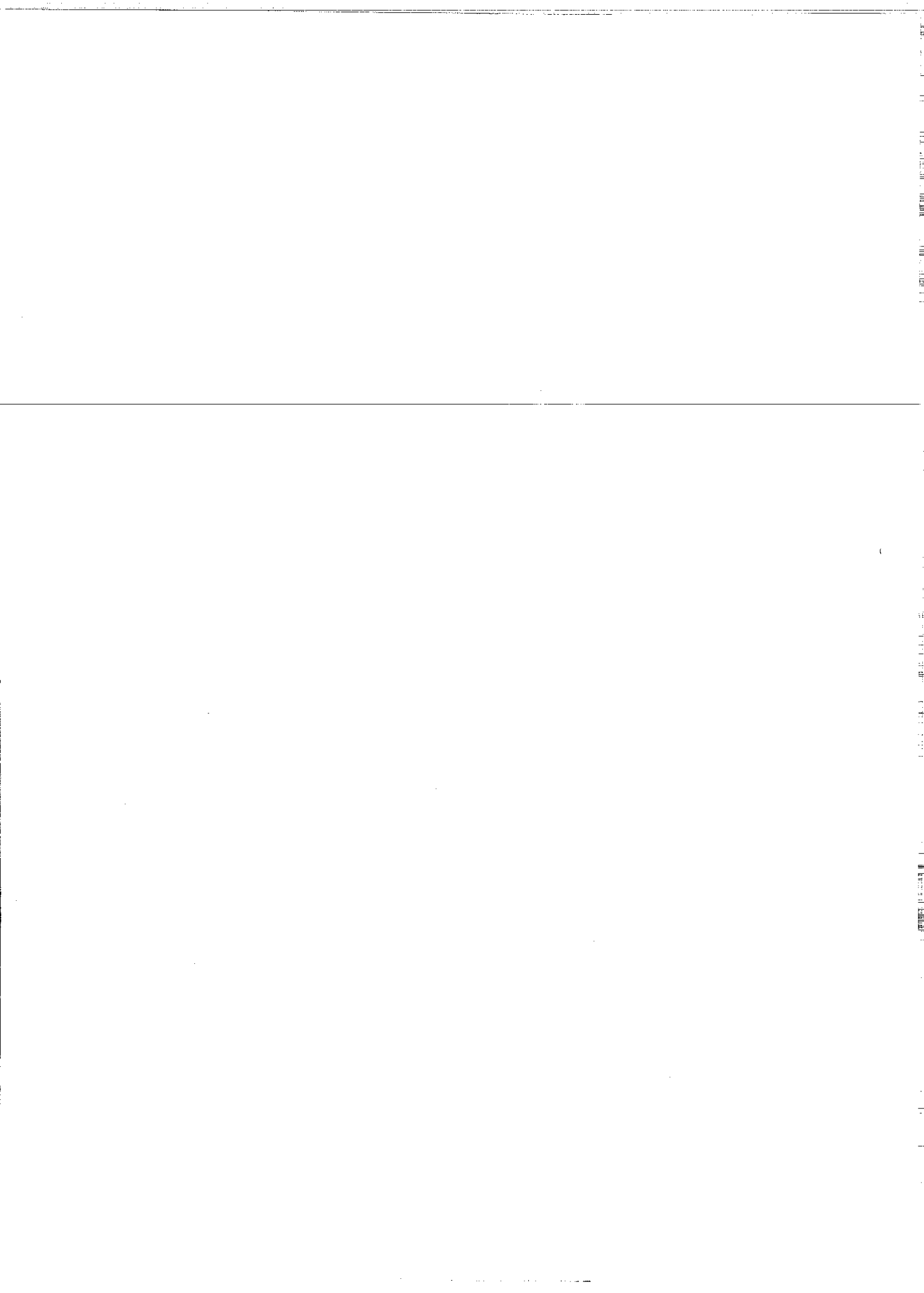
Table II -- The effect of pretreatment (-30 minutes) with
either haloperidol (HAL) or cyproheptadine HCl
(CYP) on the body temperature effects of
intraperitoneal apomorphine HCl (APO).

	Mean body temperature $^{\circ}C \pm 1.0$ SEM		
Time, min.	APO 0.5 mg/kg (N=14)	HAL 0.5 mg/kg followed by APO 0.5 mg/kg (N=8)	CYP 0.5 mg/kg followed by APO 0.5 mg/kg (N=10)
0[a]	36.83 ± 0.15	36.73 ± 0.18	37.11 ± 0.11
+15	36.44 ± 0.16	37.06 ± 0.19	36.60 ± 0.17
+30	36.32 ± 0.15	36.95 ± 0.18	36.54 ± 0.22
+45	36.46 ± 0.13	36.80 ± 0.20	36.68 ± 0.19
+60	36.59 ± 0.14	36.81 ± 0.20	36.75 ± 0.18
+75	36.73 ± 0.15	36.88 ± 0.19	36.86 ± 0.17
+90	36.76 ± 0.17	36.89 ± 0.18	36.88 ± 0.13

[a]Zero time values for the three treatment groups were
checked for homogenity using Dunnett's $\underline{t}$ test, and no
significant difference ($\underline{P} < 0.05$) was found (pooled
$s^2 = 0.2494$, d.f.=29).
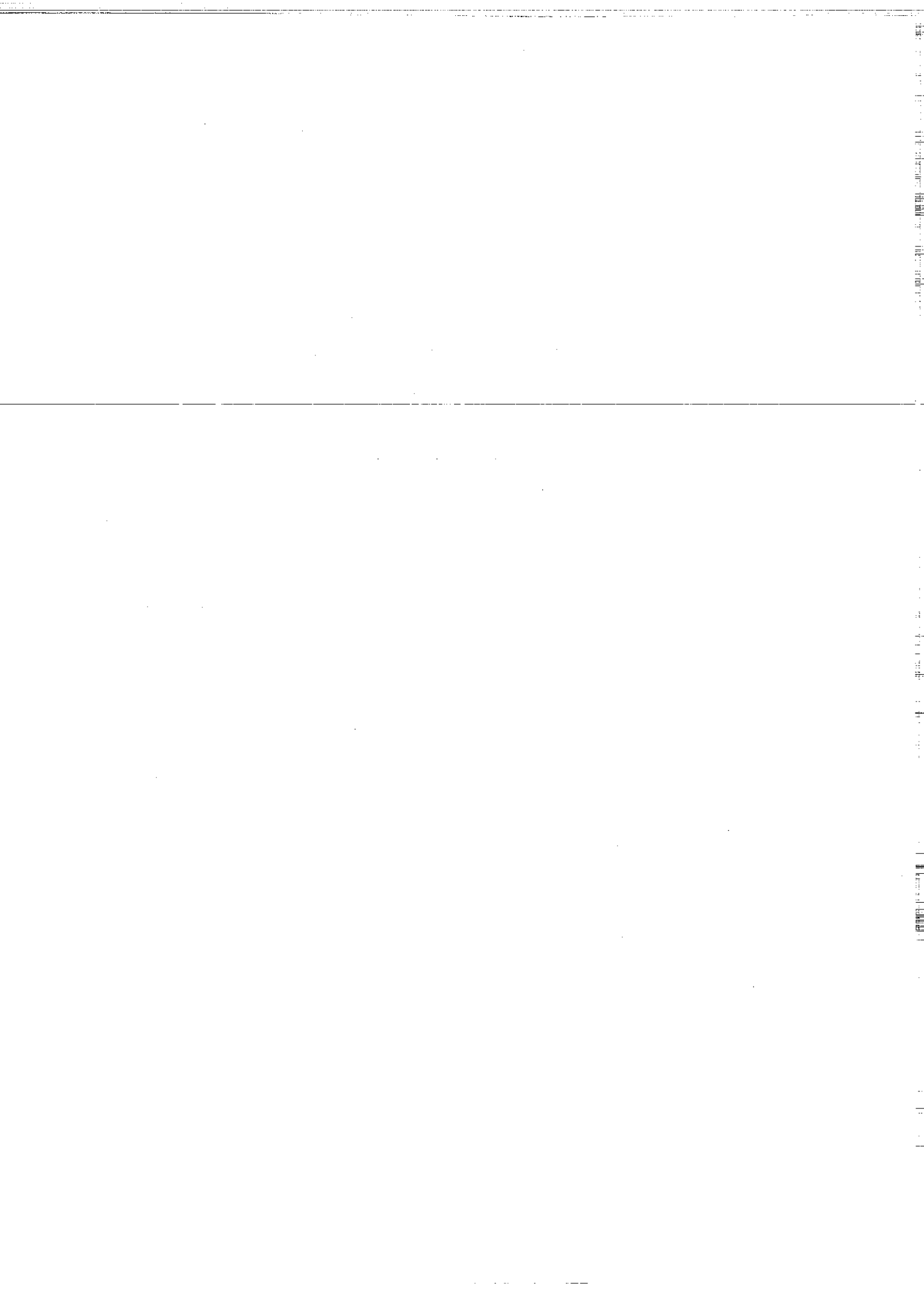
Table III -- (Continued)

Time, min.	Mean body temperature $^{\circ}C \pm 1.0$ SEM	
	CIN 5.0 mg/kg followed by APO 2.0 mg/kg (N=12)	PCPA 300 mg/kg followed by APO 2.0 mg/kg (N=9)
0	36.66 ± 0.21	37.81 ± 0.10
+15	36.21 ± 0.31	36.74 ± 0.27
+30	36.13 ± 0.31	36.61 ± 0.28
+45	36.27 ± 0.30	36.73 ± 0.26
+60	36.50 ± 0.26	37.04 ± 0.22
+75	36.63 ± 0.20	37.36 ± 0.11
+90	36.73 ± 0.17	37.59 ± 0.09
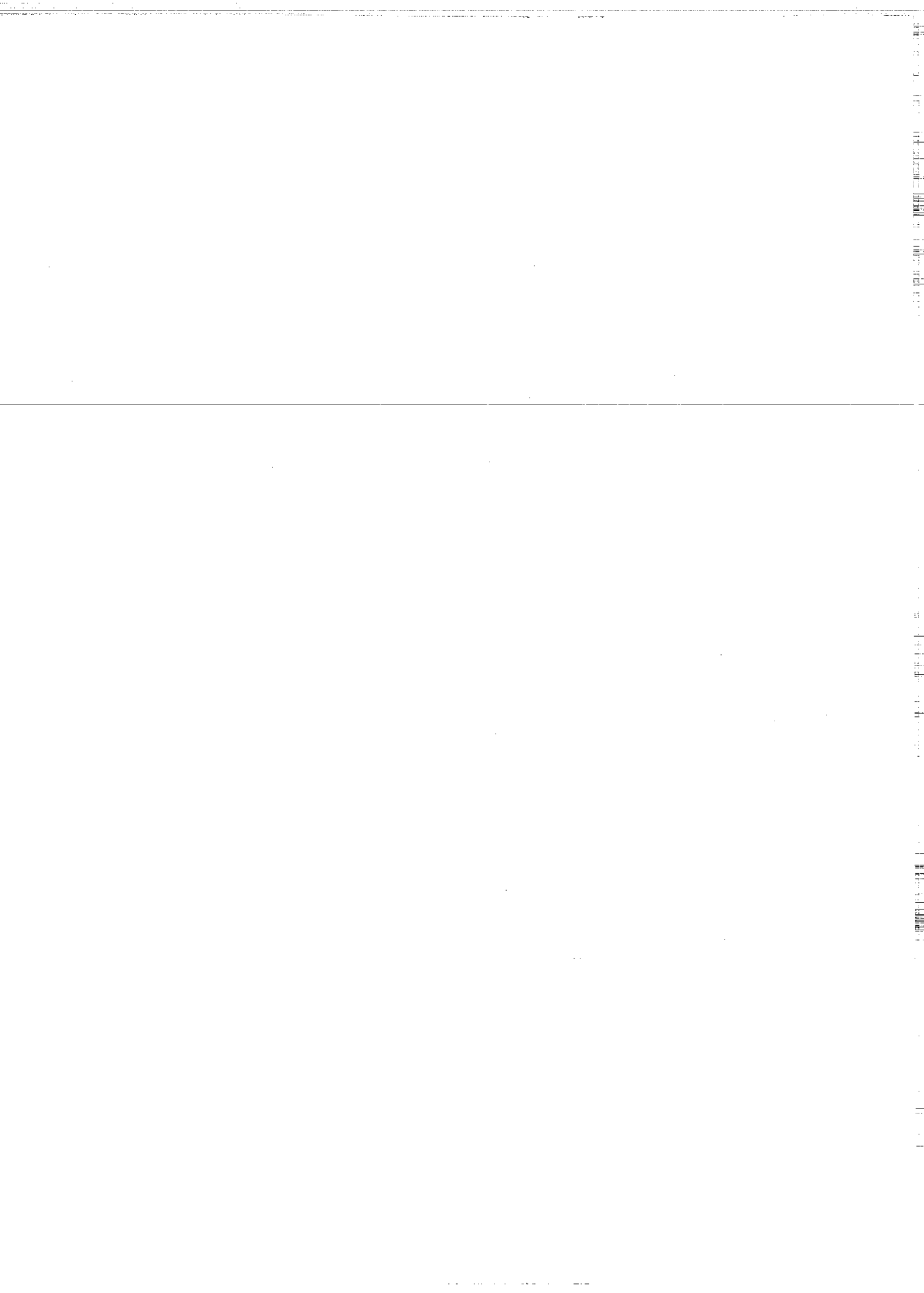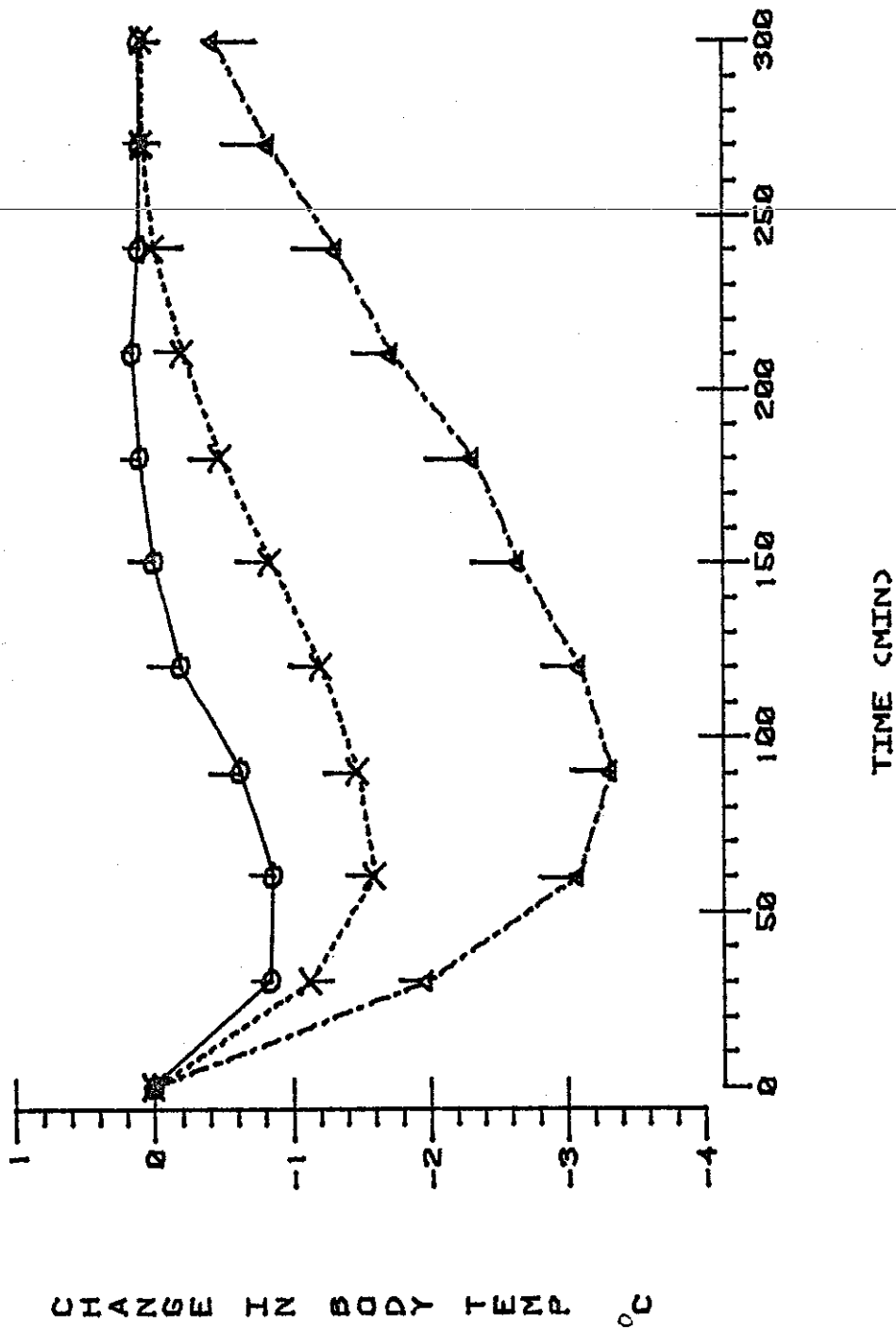
Table IV -- The effect of pretreatment (-30 minutes) with either haloperidol (HAL) or cyproheptadine HCl (CYP) on the body temperature effects of intraperitoneal lergotrile mesylate (LER).

	Mean body temperature $^{\circ}C \pm 1.0$ SEM		
Time, min.	LER 0.3 mg/kg (N=9)	HAL 0.5 mg/kg followed by LER 0.3 mg/kg (N=8)	CYP 0.5 mg/kg followed by LER 0.3 mg/kg (N=9)
0^a	36.17 ± 0.22	36.98 ± 0.26	36.94 ± 0.12
+30	35.33 ± 0.19	36.88 ± 0.23	35.93 ± 0.19
+60	35.31 ± 0.20	36.93 ± 0.20	35.74 ± 0.18
+90	35.64 ± 0.23	36.94 ± 0.23	36.00 ± 0.12
+120	35.98 ± 0.24	36.80 ± 0.24	36.26 ± 0.11
+150	36.17 ± 0.23	36.83 ± 0.25	36.51 ± 0.16
+180	36.27 ± 0.18	36.98 ± 0.20	36.67 ± 0.12
+210	36.32 ± 0.21	37.09 ± 0.17	36.76 ± 0.09
+240	36.28 ± 0.24	37.01 ± 0.17	36.78 ± 0.08
+270	36.31 ± 0.19	36.88 ± 0.20	36.89 ± 0.09
+300	36.19 ± 0.16	37.04 ± 0.12	36.90 ± 0.09

[a]Zero time values for the three treatment groups were checked for homogenity using Dunnett's $\underline{t}$ test, and both the HAL and the CYP pretreated groups were significantly different ($P < 0.05$) from the LER control group (pooled $s^2 = 0.3660$, $\overline{d}.f. = 23$).

Table V -- (Continued)

	Mean body temperature $^{\circ}$C $\pm$ 1.0 SEM	
Time, min.	CIN 5.0 mg/kg followed by LER 1.0 mg/kg (N=10)	PCPA 300 mg/kg followed by LER 1.0 mg/kg (N=11)
0[a]	36.92 $\pm$ 0.16	37.44 $\pm$ 0.12
+30	34.99 $\pm$ 0.14	35.95 $\pm$ 0.21
+60	34.45 $\pm$ 0.23	35.28 $\pm$ 0.28
+90	34.63 $\pm$ 0.24	35.45 $\pm$ 0.24
+120	35.47 $\pm$ 0.31	35.65 $\pm$ 0.22
+150	36.18 $\pm$ 0.31	36.14 $\pm$ 0.21
+180	36.88 $\pm$ 0.26	36.65 $\pm$ 0.19
+210	36.92 $\pm$ 0.19	37.05 $\pm$ 0.14
+240	36.84 $\pm$ 0.17	37.25 $\pm$ 0.08
+270	36.91 $\pm$ 0.13	37.30 $\pm$ 0.12
+300	36.94 $\pm$ 0.12	37.41 $\pm$ 0.11

Table VI —— The effect of pretreatment (-30 minutes) with either haloperidol (HAL) or cyproheptadine HCl (CYP) on the body temperature effects of intraperitoneal lergotrile mesylate (LER).

	Mean body temperature $^{\circ}$C $\pm$ 1.0 SEM		
Time, min.	LER 3.0 mg/kg (N=10)	HAL 0.5 mg/kg followed by LER 3.0 mg/kg (N=9)	CYP 0.5 mg/kg followed by LER 3.0 mg/kg (N=9)
0[a]	36.33 $\pm$ 0.21	36.52 $\pm$ 0.24	37.21 $\pm$ 0.16
+30	34.36 $\pm$ 0.17	34.96 $\pm$ 0.32	35.18 $\pm$ 0.24
+60	33.25 $\pm$ 0.17	34.99 $\pm$ 0.33	34.03 $\pm$ 0.28
+90	33.01 $\pm$ 0.21	35.48 $\pm$ 0.34	33.71 $\pm$ 0.25
+120	33.24 $\pm$ 0.23	35.94 $\pm$ 0.33	33.86 $\pm$ 0.26
+150	33.68 $\pm$ 0.28	36.28 $\pm$ 0.28	34.11 $\pm$ 0.25
+180	34.01 $\pm$ 0.30	36.49 $\pm$ 0.21	34.44 $\pm$ 0.25
+210	34.61 $\pm$ 0.31	36.50 $\pm$ 0.20	34.98 $\pm$ 0.29
+240	35.01 $\pm$ 0.30	36.59 $\pm$ 0.20	35.41 $\pm$ 0.28
+270	35.50 $\pm$ 0.30	36.63 $\pm$ 0.21	35.78 $\pm$ 0.25
+300	35.90 $\pm$ 0.27	36.62 $\pm$ 0.18	36.06 $\pm$ 0.23

[a]Zero time values for the three treatment groups were checked for homogenity using Dunnett's t test, and only the CYP pretreated group was significantly different ($p < 0.05$) from the LER control group (pooled s^2=0.3914, d.f.=25)
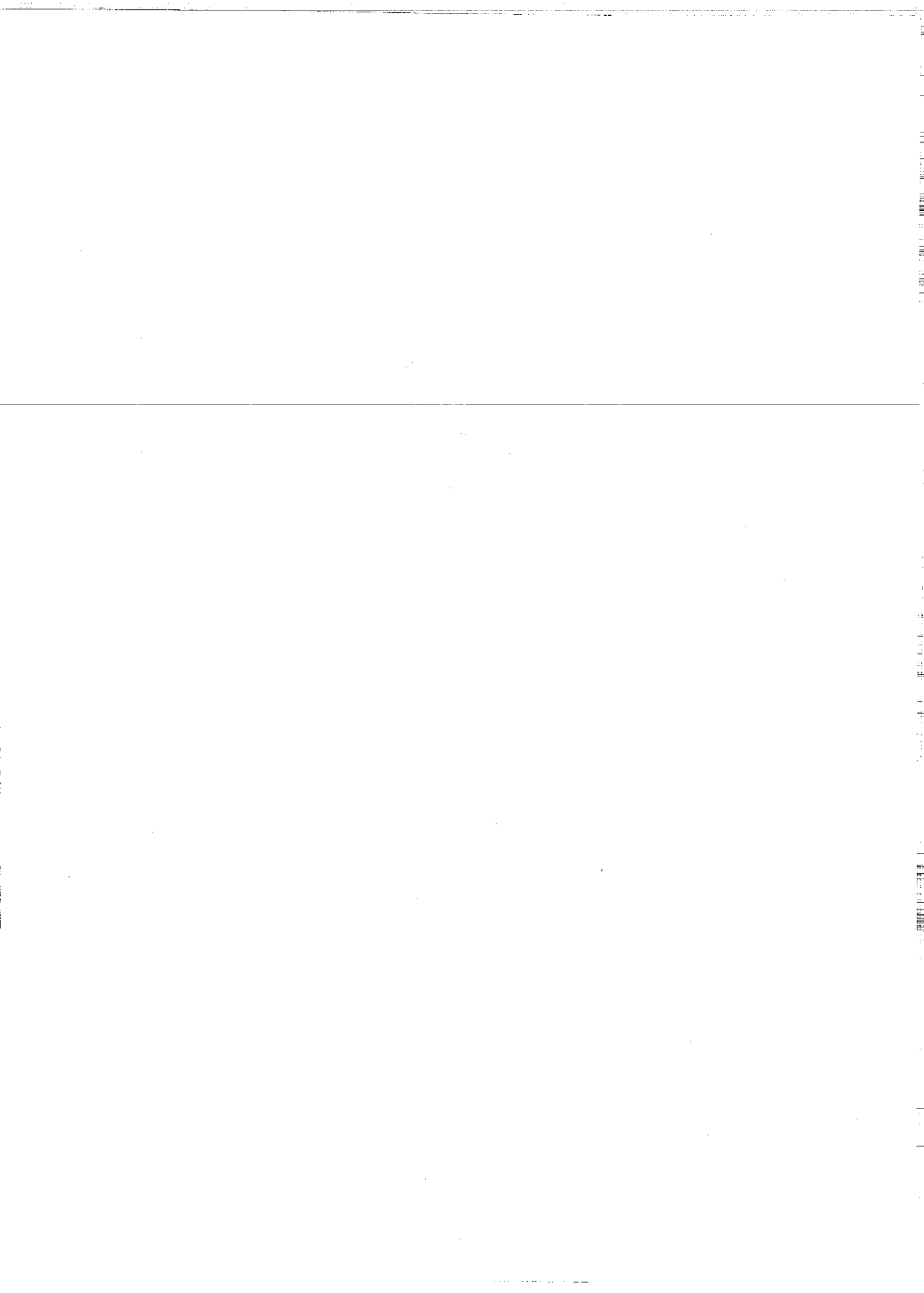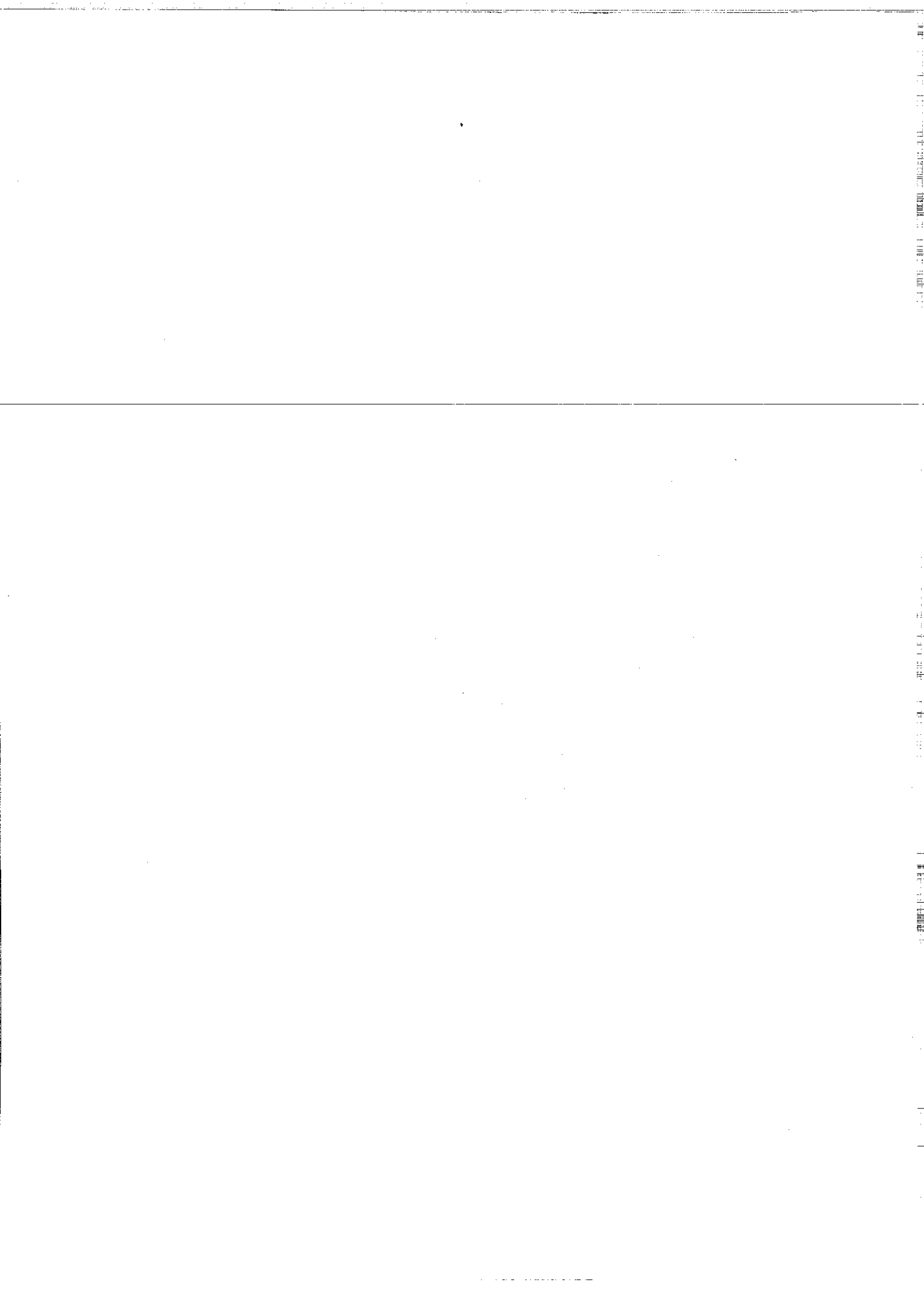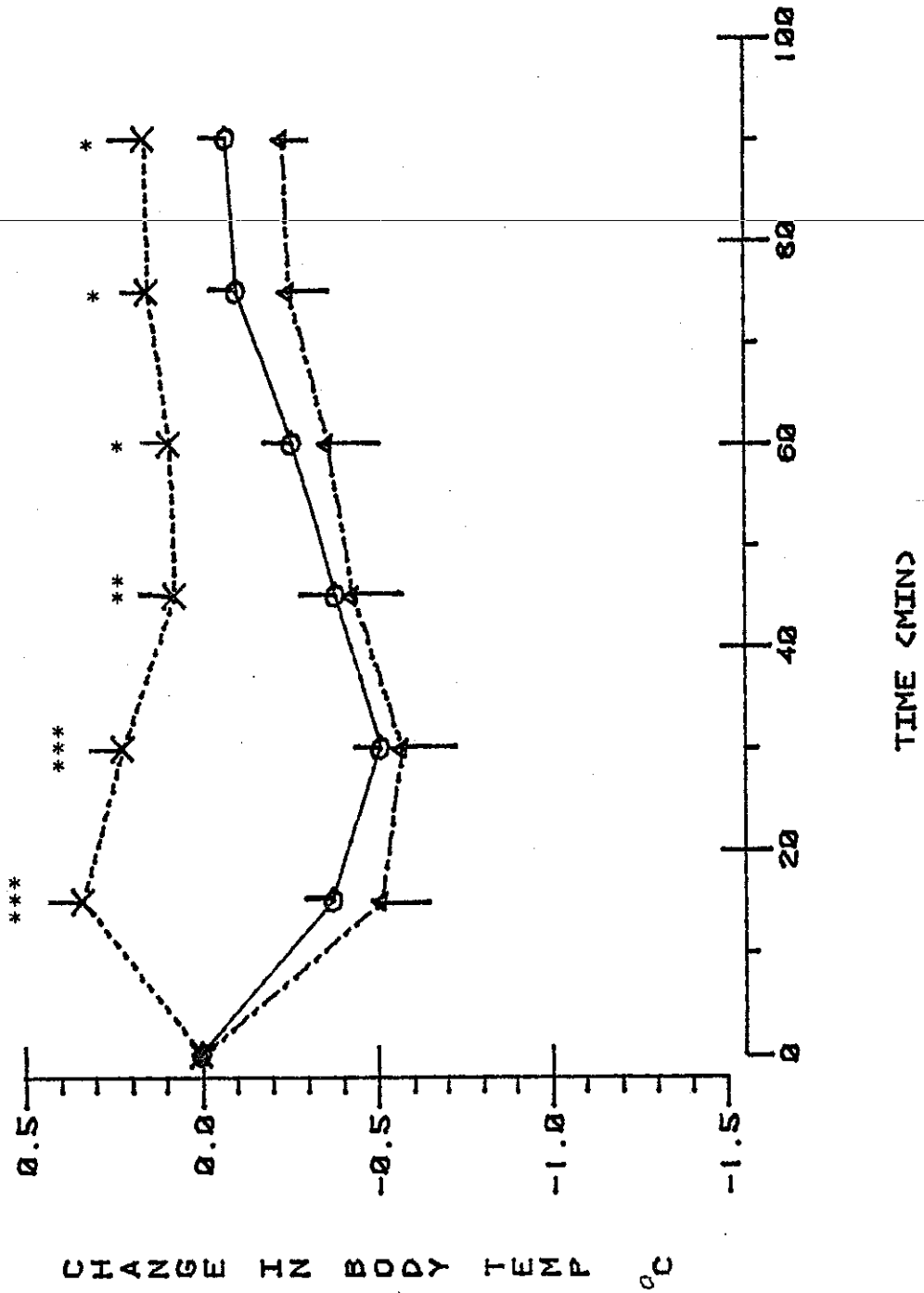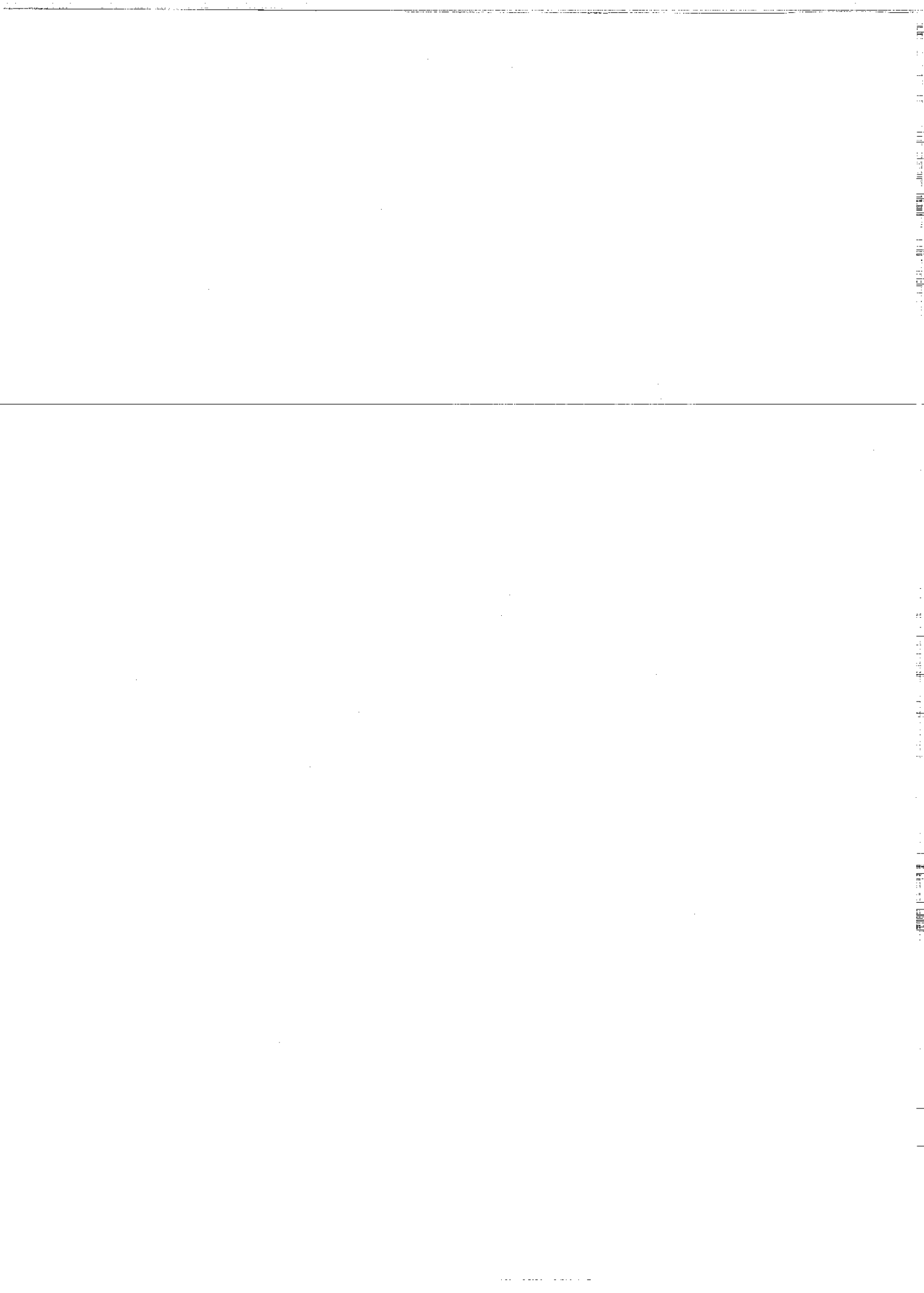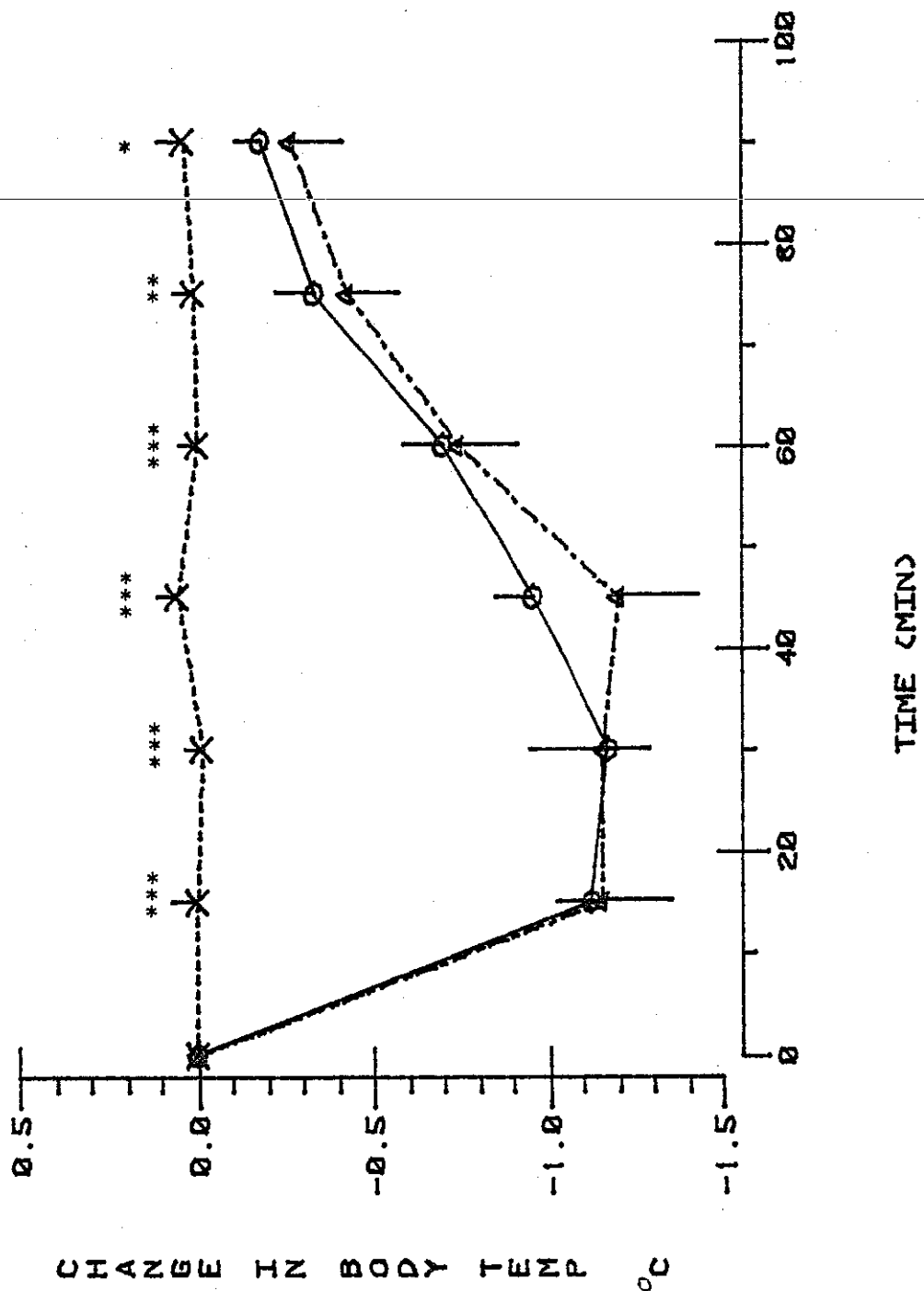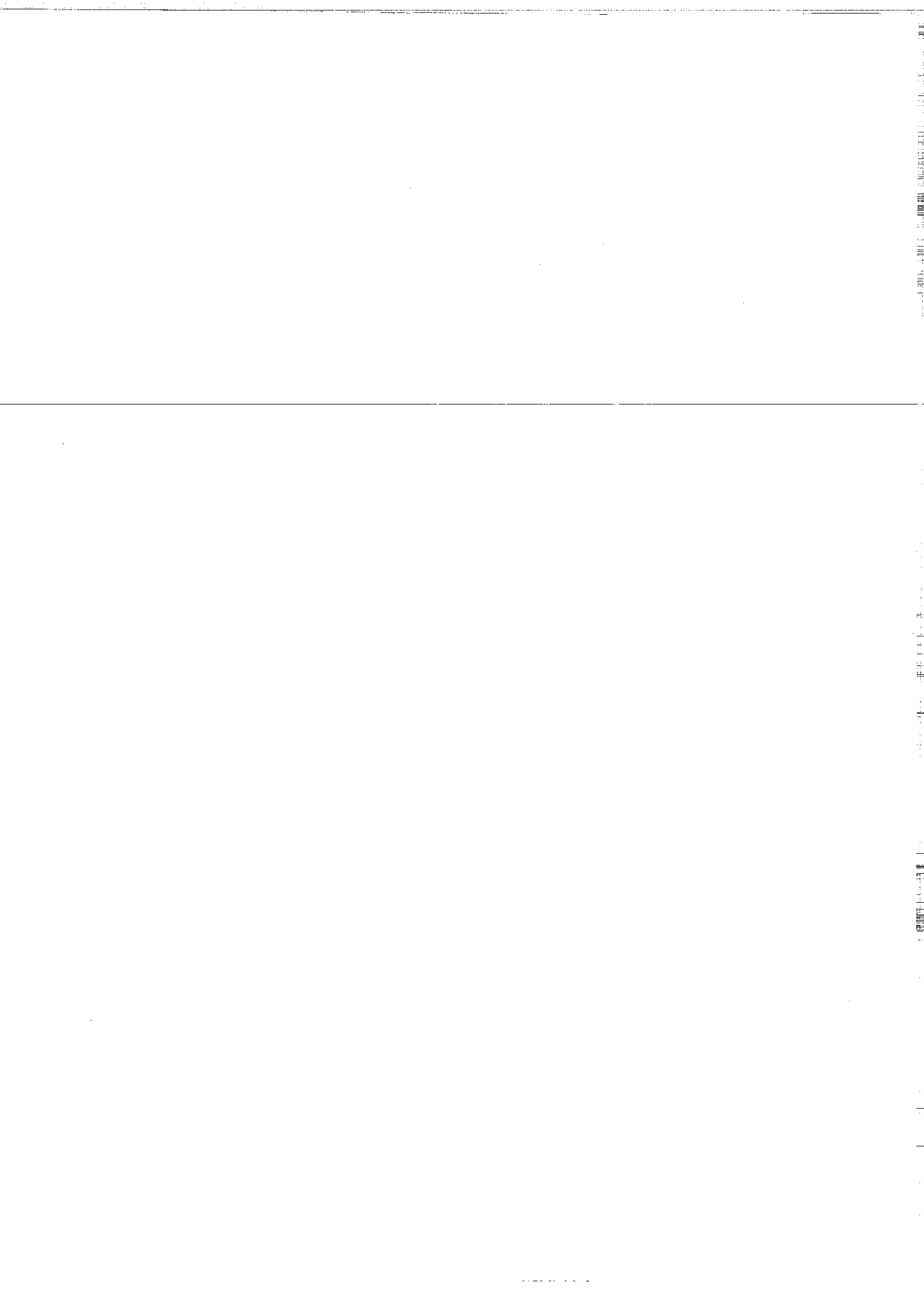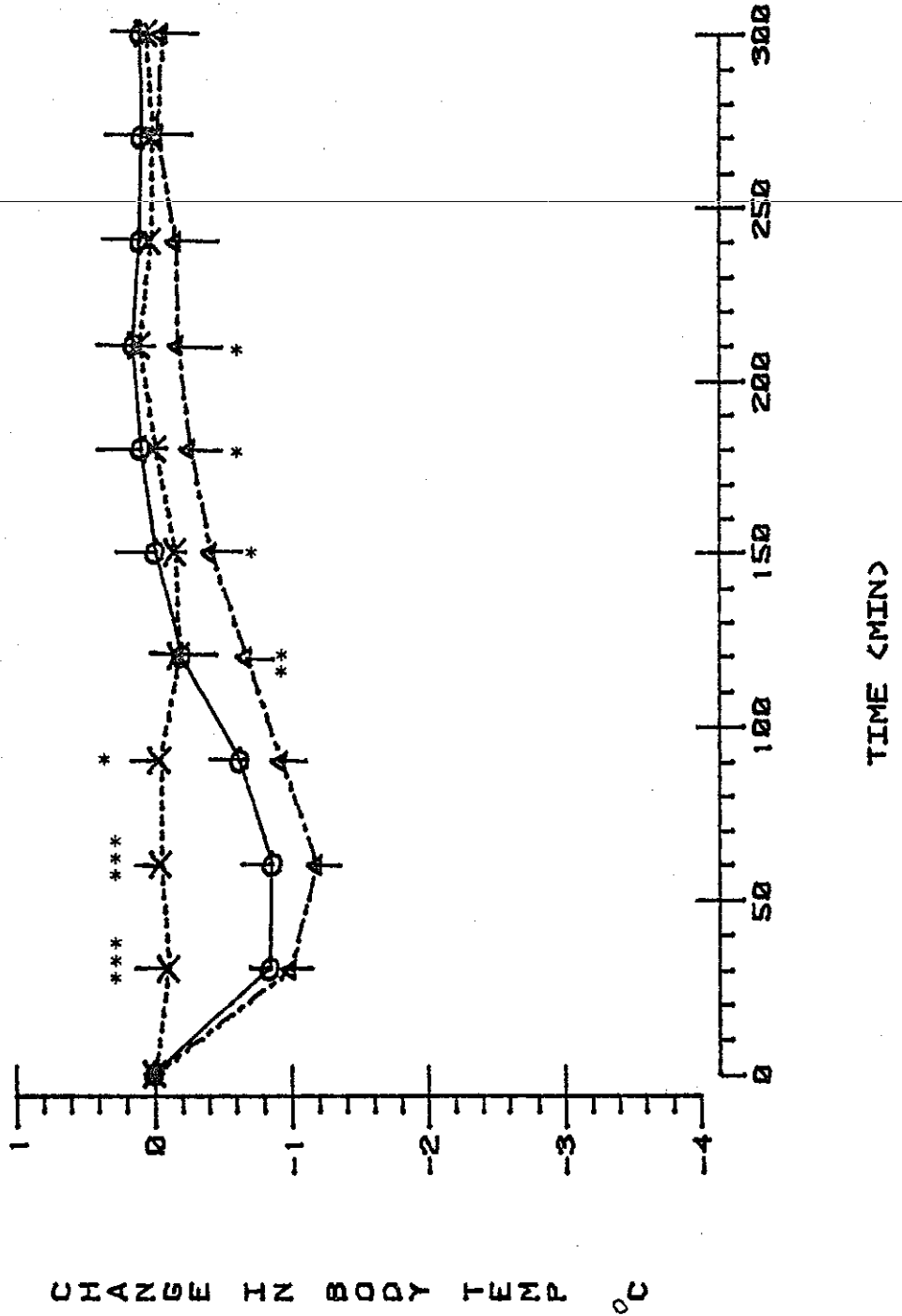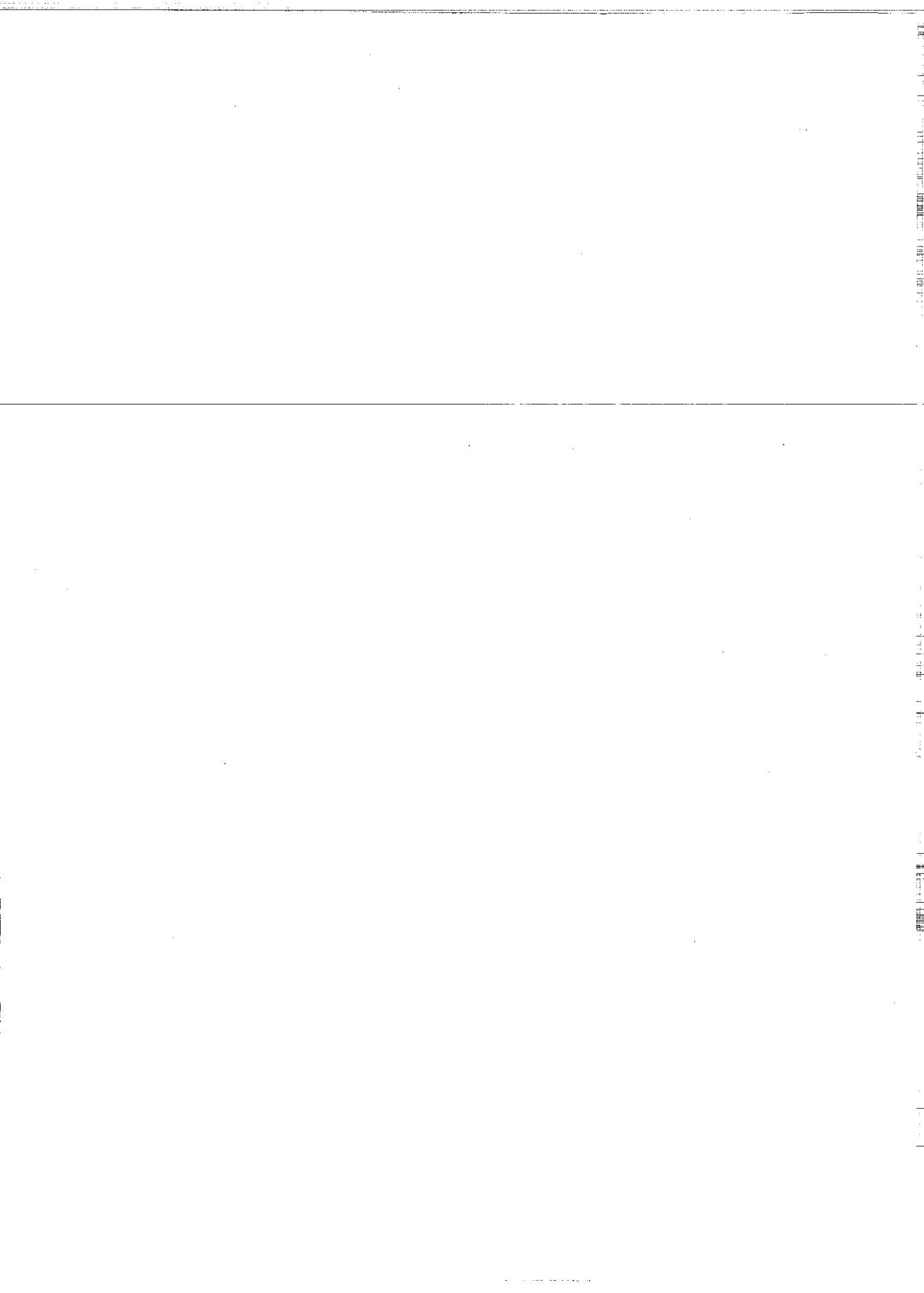
TIME (MIN)

CHANGE IN BODY TEMP °C

O LER 1.0
X HAL/LER
△ CYP/LER

O □ H2O
X HAL 0.5
△ CYP 0.5
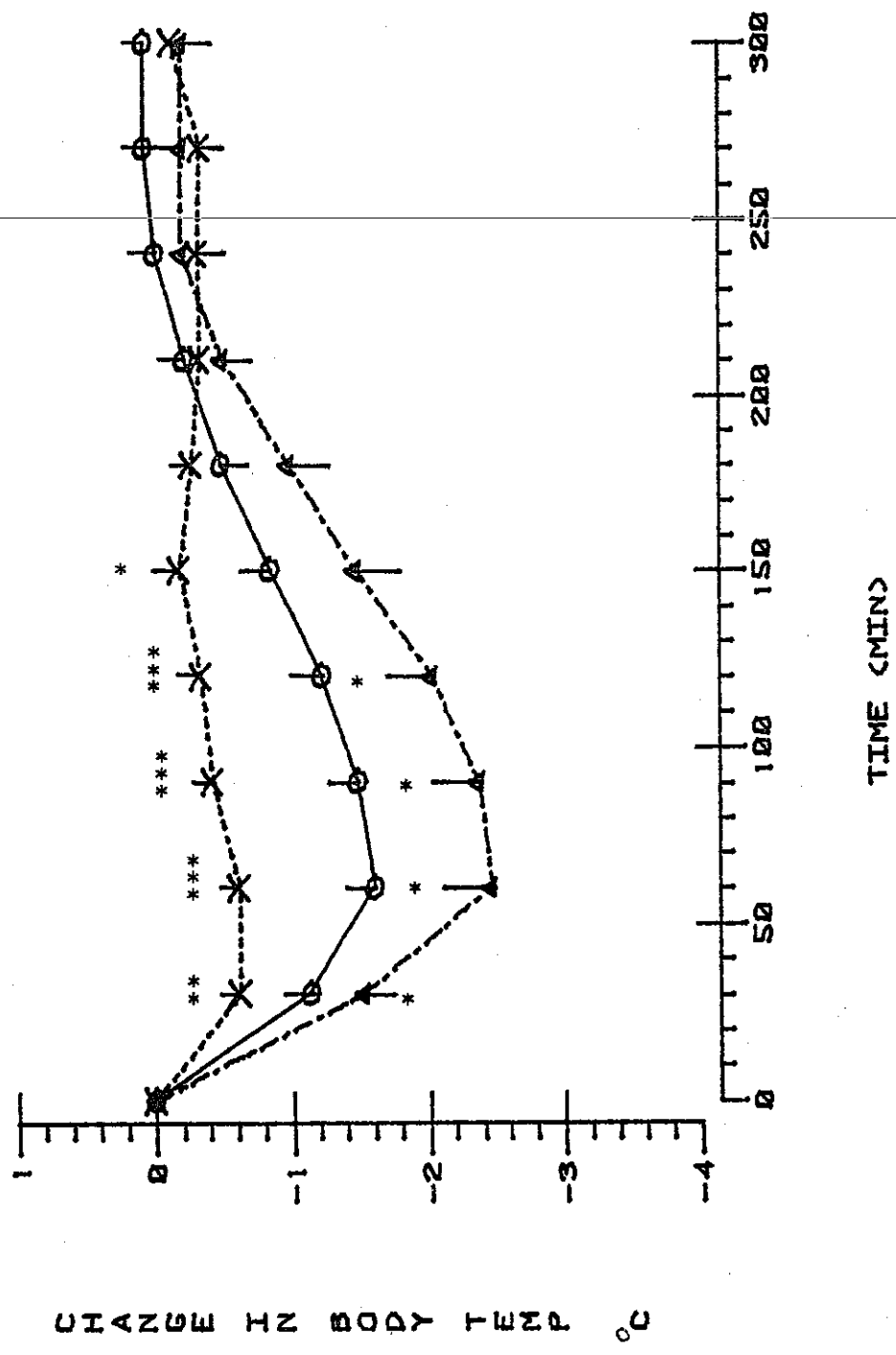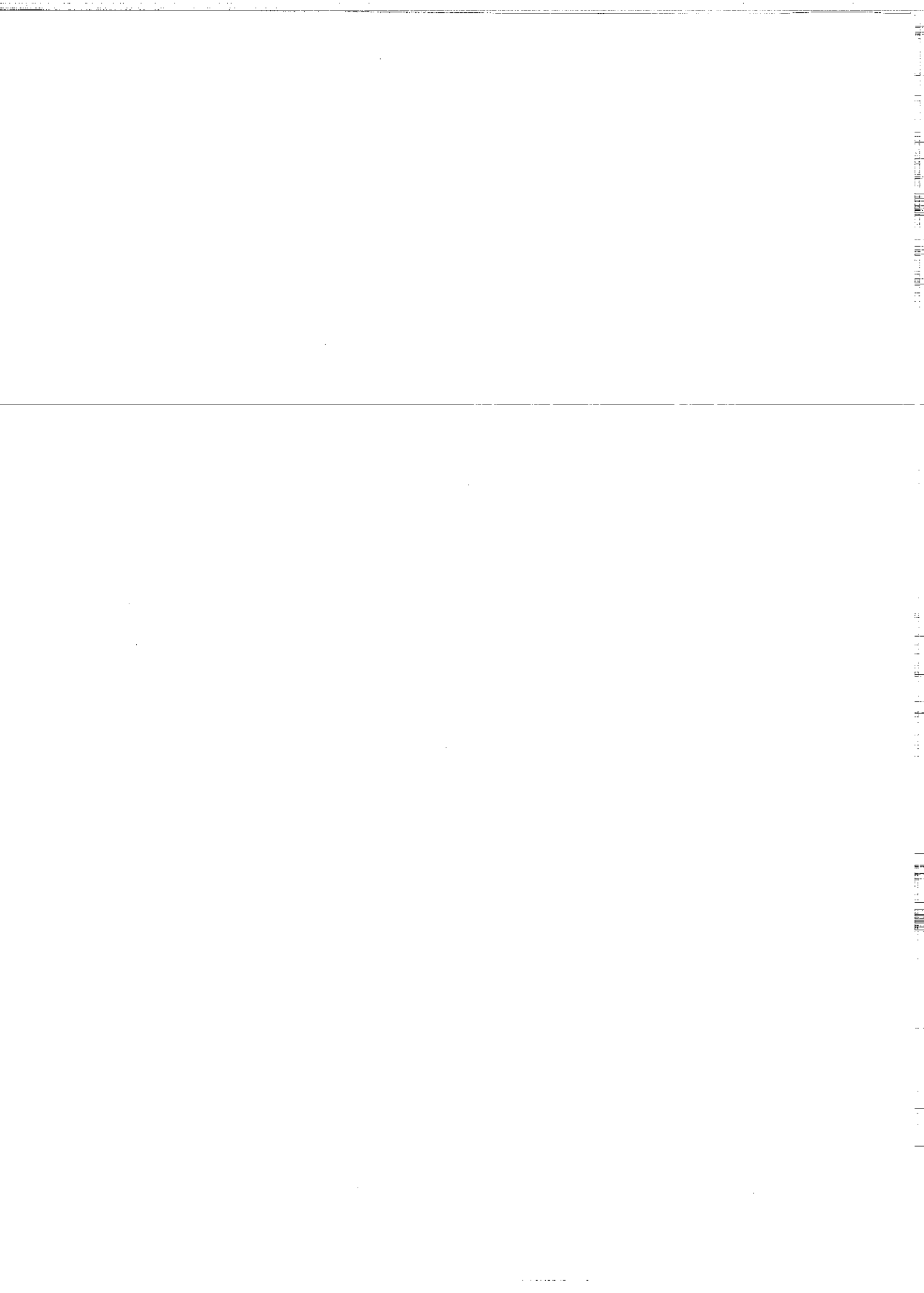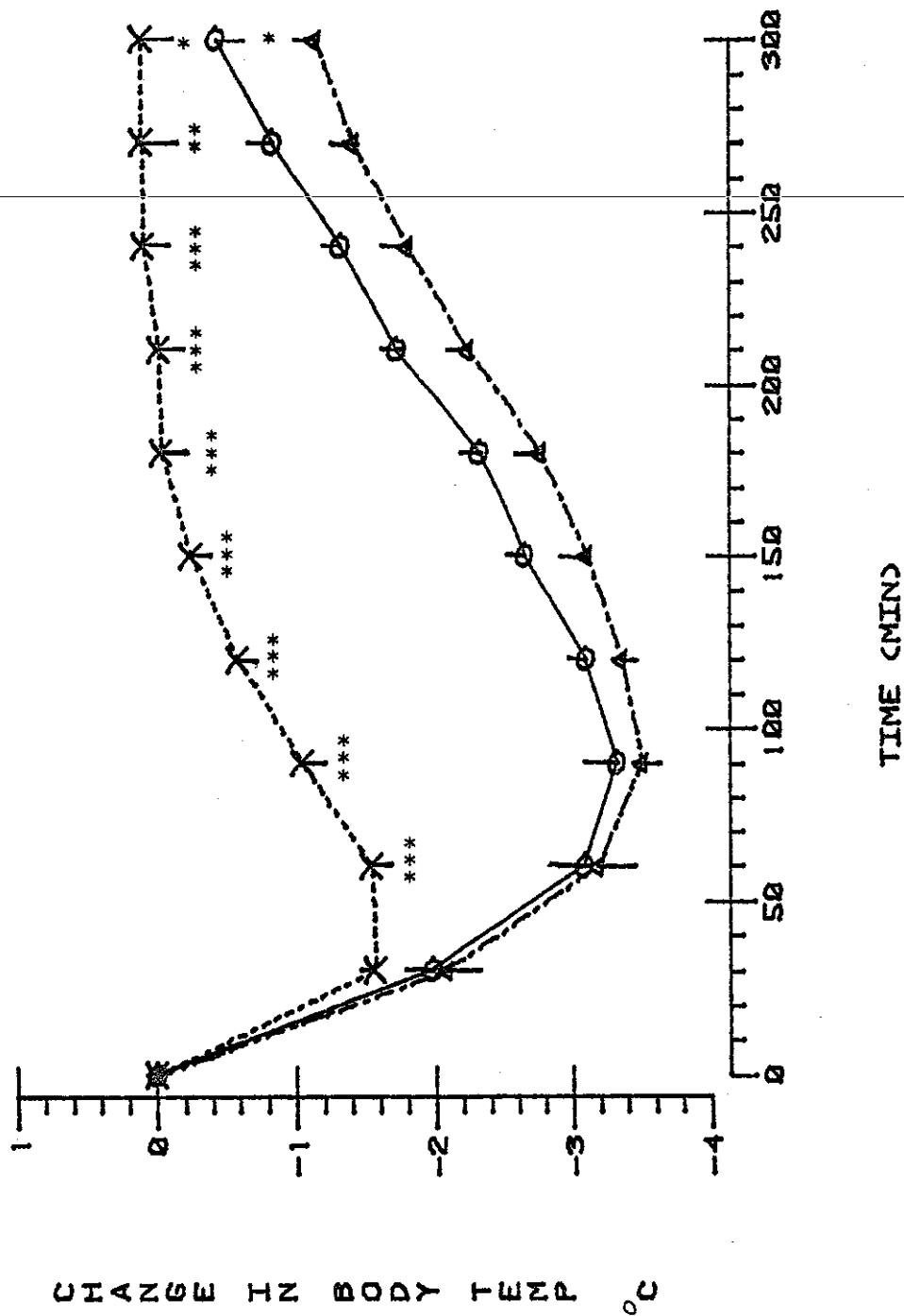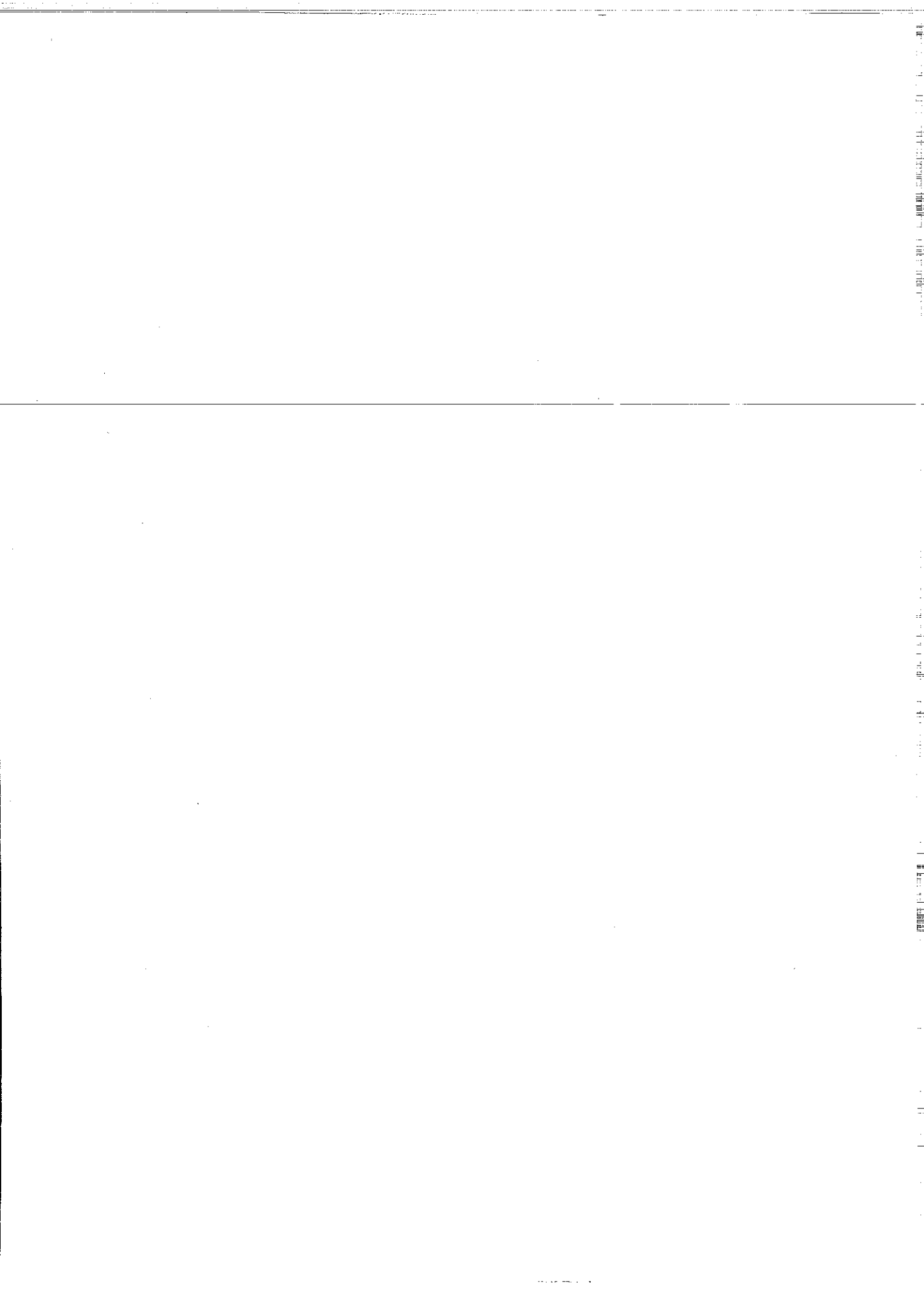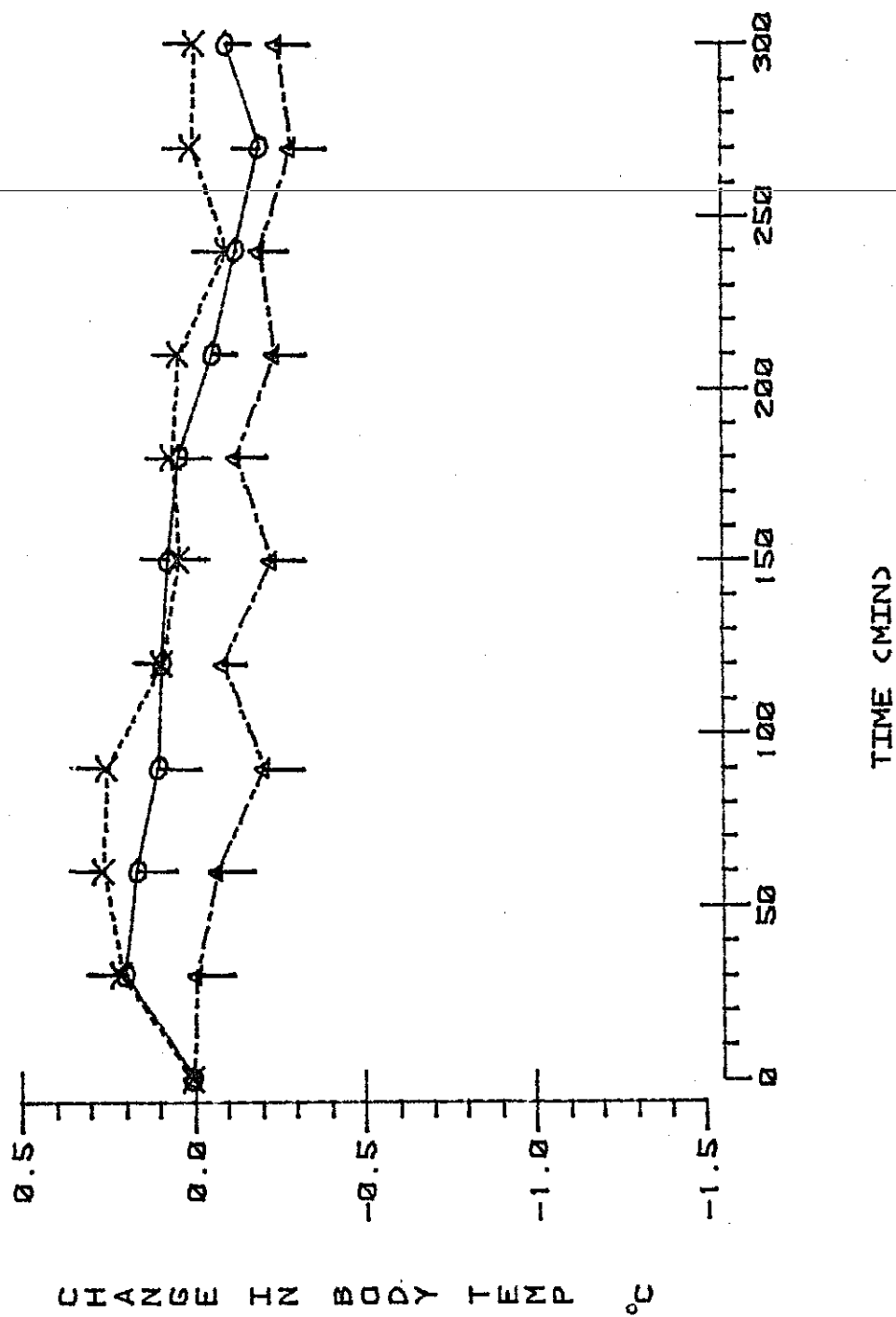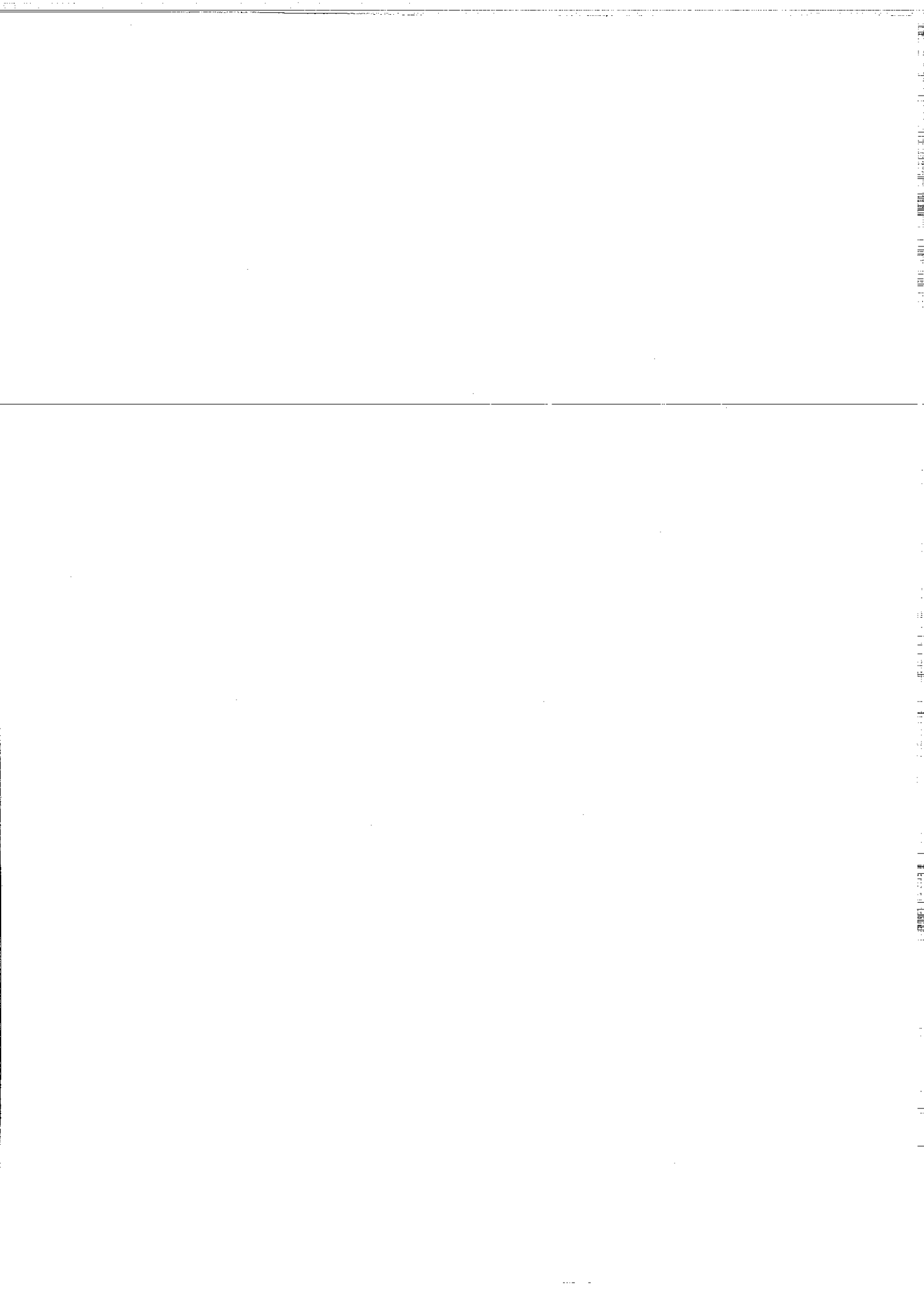
TIME (MIN)

CHANGE IN BODY TEMP °C
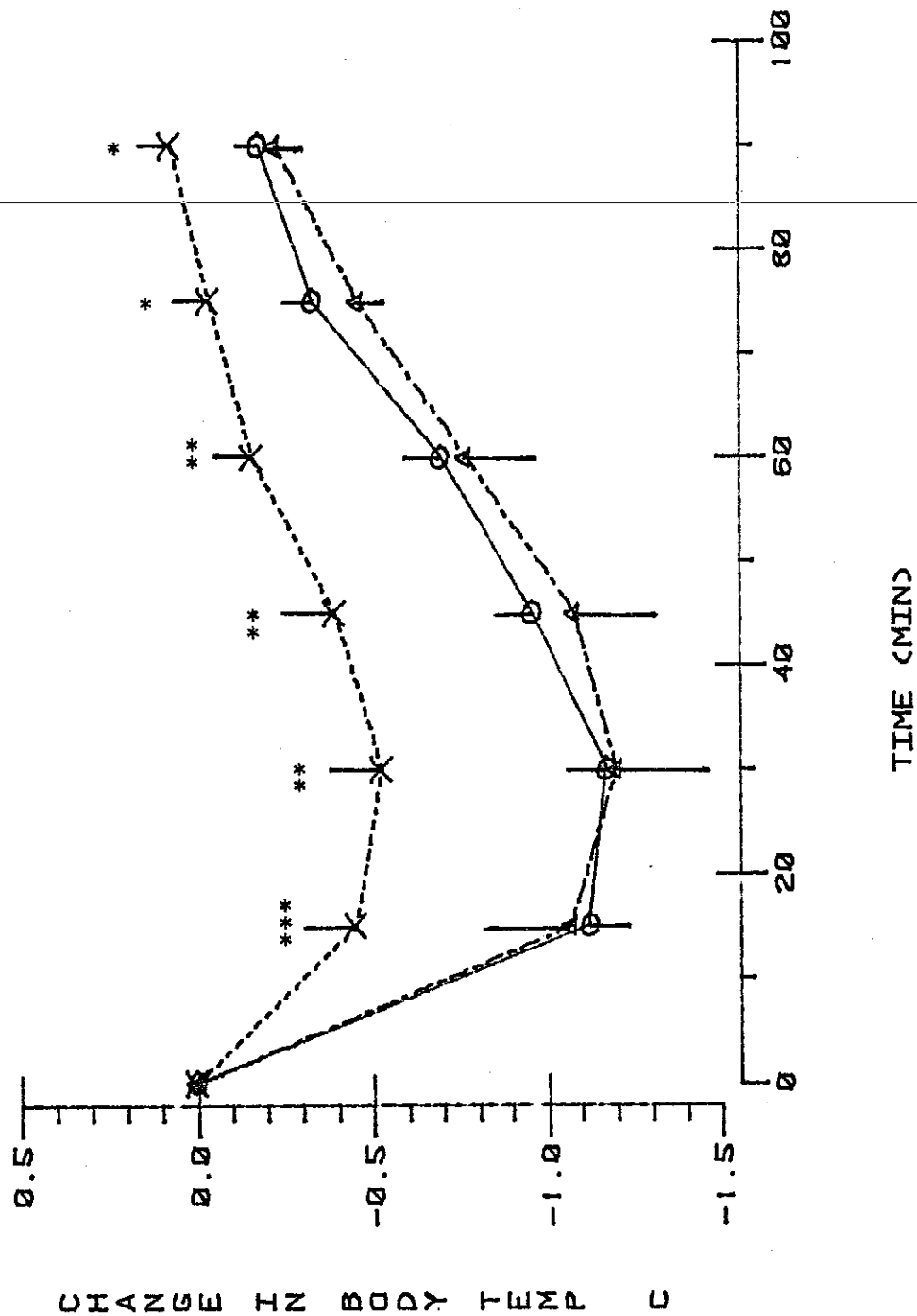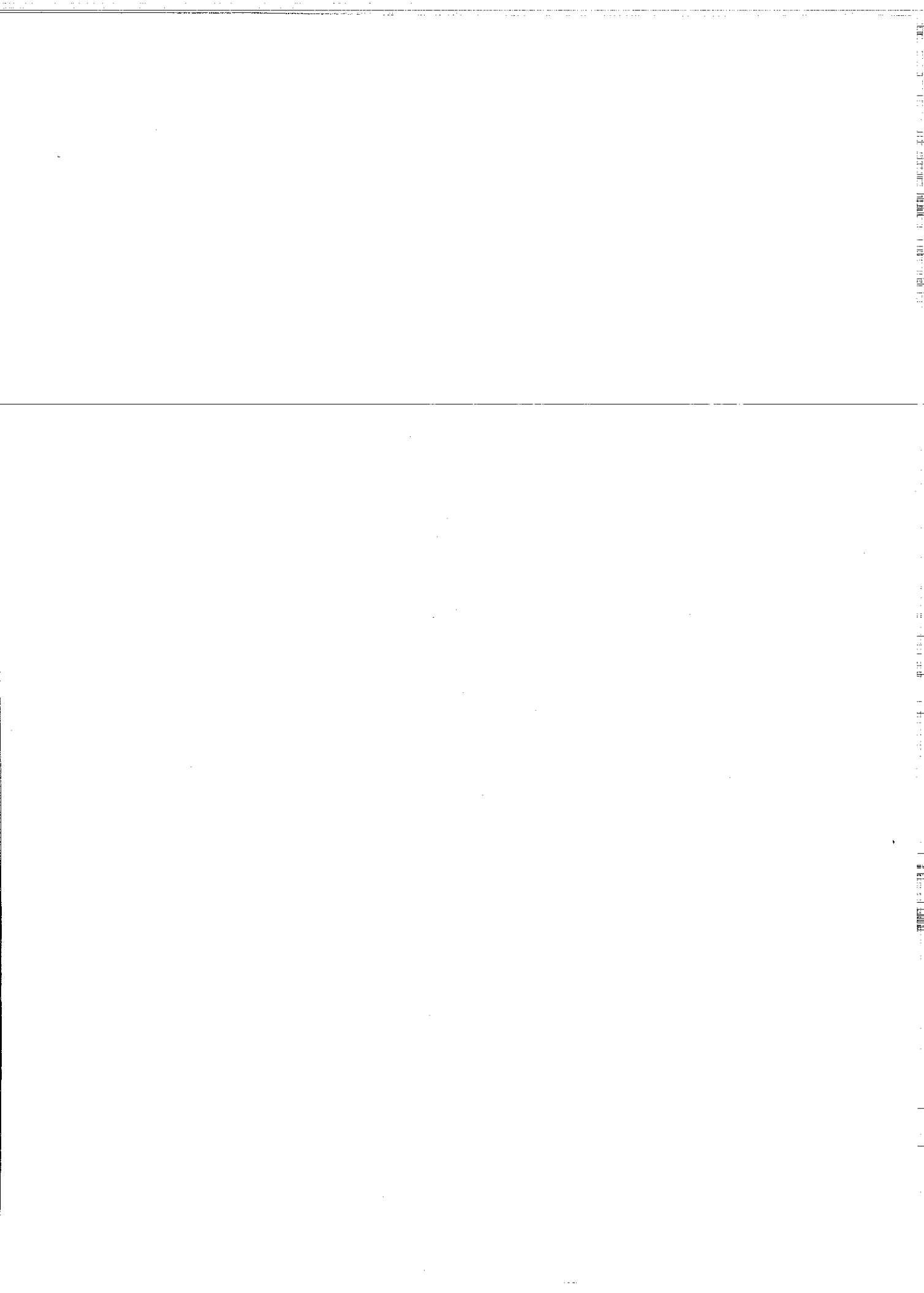
OLER 1.0
X CIN/LER
Δ PCPA/LER
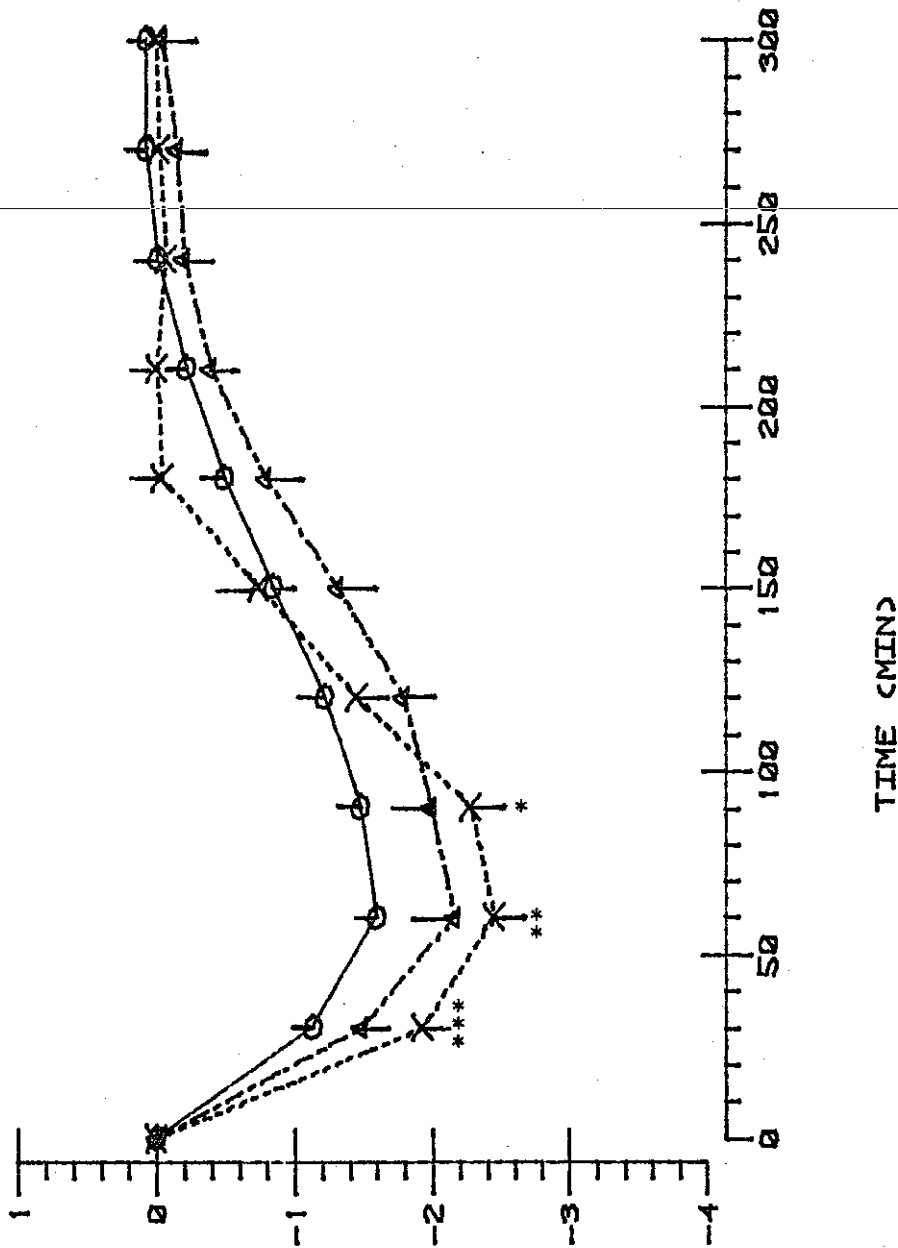
TIME (MIN)

CHANGE IN BODY TEMP C

ester HCl 300 mg/kg reduced whole brain serotonin content to 17 percent of water-pretreated control rats in 48 hours (Table VII). Serotonin depletion with parachlorophenyl-alanine apparently has no effect on apomorphine-induced hypothermia (Fig. 10) and may tend to potentiate lergotrile-induced hypothermia (not statistically significant, see Fig. 11).

2. Stereotyped behavior

Apomorphine and lergotrile at low doses induced stereotypy consisting of increased locomotion coupled with sniffing and repetitive head and limb movements. At these doses, apomorphine produced continuous locomotor activity and head and limb movements while the locomotor activity and repetitive movements induced by lergotrile were discontinuous, suggesting that apomorphine may stimulate the low-intensity components of stereotypy to a greater extent than lergotrile. Increasing the dose of apomorphine or lergo-trile replaced locomotor activity with intermittent biting, gnawing or licking mouth movements. High doses of apomorphine or lergotrile evoked continuous (at least 30 seconds without stopping) biting, gnawing or licking mouth movements. Mouth movements induced by lergotrile mesylate 1.0 mg/kg were very continuous, frequently lasting several minutes without interruption.

The results of haloperidol and cyproheptadine pretreatments on apomorphine- and lergotrile-induced stereotypy are summarized in Table VIII. Haloperidol produced slight sedation

Table VII -- The effect of pretreatment (-48 hours) with
either intraperitoneal double-distilled
water (DH2O) or parachlorophenylalanine
methyl ester hydrochloride (PCPA) on the
whole brain serotonin content of male rats.

Treatment, dosage	Mean ± 1.0 SEM	t	P
DH2O, 2.0 ml/kg (N=6)	0.465 ± 0.023 ug/g		
PCPA, 300 mg/kg (N=6)	0.081 ± 0.017 ug/g	13.36	<0.001

Table VIII -- The effect of pretreatment (-30 minutes) with either haloperidol or cyproheptadine HCl on stereotyped behavior produced by intraperitoneal apomorphine HCl or lergotrile mesylate in male rats..

Treatment	mg/kg	Total stereotypy score $\pm$ 1.0 SEM (N)		
		Apomorphine HCl 0.5 mg/kg	Apomorphine HCl 2.0 mg/kg	Lergotrile mesylate 1.0 mg/kg
Control (H$_2$O)	-	12.0 $\pm$ 1.8 (13)	33.2 $\pm$ 3.1 (11)	24.2 $\pm$ 2.7 (15)
Haloperidol	0.25	2.7 $\pm$ 0.5[b] (7)	2.0 $\pm$ 0.4[b] (7)	-
Haloperidol	0.5	1.9 $\pm$ 1.1[b] (9)	0.9 $\pm$ 0.3[b] (9)	5.3 $\pm$ 1.1[b] (9)
Haloperidol	1.0	-	-	4.4 $\pm$ 1.2[b] (9)
Cyproheptadine HCl	0.5	8.7 $\pm$ 2.7 (7)	26.3 $\pm$ 4.7 (12)	-
Cyproheptadine HCl	1.0	9.1 $\pm$ 1.4 (10)	18.1 $\pm$ 4.9[a] (10)	29.9 $\pm$ 3.2 (10)
Cyproheptadine HCl	2.0	-	-	35.6 $\pm$ 3.4[a] (9)

[a] Significantly different from control ($\underline{P} < 0.05$)
[b] Very highly significantly different from control ($\underline{P} < 0.001$)

and very highly significantly antagonized both apomorphine-
and lergotrile-induced stereotypy in a dose-related manner.
Cyproheptadine also reduced the total stereotypy score pro-
duced by apomorphine in a dose-related manner. This antag-
onism became significant as the doses of apomorphine and
cyproheptadine were raised. Cyproheptadine alone produced
no behavioral effects. Cyproheptadine had an opposite
effect on lergotrile-induced stereotypy. A significant
potentiation of lergotrile-induced stereotypy was observed
as the pretreatment dose of cyproheptadine HCl was increased
to 2.0 mg/kg.

Discussion

The present study indicates that differences exist as
to the effects of known serotonin antagonists (cyproheptadine
and cinanserin) upon the hypothermic and stereotypic effects
of apomorphine and lergotrile. Pretreatment with cyprohep-
tadine had no effect on apomorphine-induced hypothermia
while it potentiated that of lergotrile, and pretreatment
with cyproheptadine attenuated apomorphine-induced stereo-
typy while potentiating lergotrile-induced stereotypy. Pre-
treatment with cinanserin potentiated lergotrile-induced
hypothermia while antagonizing apomorphine-induced hypotherm-
ia. This same pattern was observed with cinanserin in
regard to apomorphine- and lergotrile-induced stereotypy.

Despite the differences that serotonin blockade appears
to have on apomorphine- and lergotrile-induced effects, the
observed effects of these drugs are probably due to some
effect on dopaminergic mechanisms. Convincing evidence in
the rat exists linking the stimulation of dopamine receptors
to hypothermia (Kruk, 1972; Fuxe and Sjoqvist, 1972) and

stereotyped behavior (Ernst, 1967; Anden, 1967). The ability
of the dopamine antagonist haloperidol to abolish the effects
of both apomorphine and lergotrile in the present experi-
ments is presumptive evidence that both apomorphine and
lergotrile exert their effects via dopamine receptors. This
is in agreement with the consistent findings in rats that
apomorphine induces hypothermia (Barnett et al., 1972; Chiel
et al., 1974; Ary et al., 1977; Cox and Lee, 1978) as well
as stereotyped behavior (Harnack, 1874; Ernst, 1967; Costall
and Naylor, 1972) and that dopamine antagonists can block
the hypothermic and stereotypic effects of apomorphine (Kruk,
1972; Fuxe and Sjoqvist, 1972; DiChiara and Gessa, 1978).
Until the present investigation, lergotrile-induced hypother-
mia and stereotypy have not been studied and these effects
have not previously been demonstrated to be attenuated
by neuroleptics. However, inhibition of unit activity of
dopamine cells by lergotrile has been reported to be antagon-
ized with haloperidol (Walters et al., 1979) and lergotrile
has been found to compete with radiolabeled haloperidol
binding sites in rat striatum (Lew et al., 1977). Addition-
ally, the hypothermic effect of another ergoline, bromo-
cryptine, has been demonstrated to be antagonized by pimo-
zide (Calne et al., 1975).

As both apomorphine and lergotrile appear to exert their
hypothermic and stereotypic effects via dopamine receptors,
the involvement of serotonin in these effects may be due to
three different possibilities. First, serotonin may be a

physiological antagonist for the hypothermia and stereotyped
behavior induced by dopaminergic stimulation. Serotonin
could exert direct opposing action on the target response
(hypothermia or stereotyped behavior) through an independent
pathway or could inhibit the dopaminergic pathways leading
to full expression of the target response. Second, serotonin
may facilitate the effects of dopaminomimetics on hypothermia
or stereotyped behavior in the rat. Serotonin would then
exist as a functional link in the final expression of dopam-
inergic stimulation, or serotonin activation alone could pro-
duce an identical response to that of dopaminergic stimula-
tion. Third, serotonin may have no effect at all upon dop-
aminergic systems since neither cyproheptadine nor cinanserin
can be classified as selective serotonin antagonists (e.g.
cyproheptadine is also a potent histamine antagonist; see
Stone et al., 1973).

The present findings suggest that serotonin antagonists
attenuate apomorphine-induced hypothermia while facilitating
lergotrile-induced hypothermia. This proposes a facilitatory
role for serotonin in apomorphine-induced hypothermia and
an antagonistic role for serotonin in lergotrile-induced
hypothermia. The results with apomorphine in the present
study are in agreement with the results of other investiga-
tors. Cox and Lee (1979) found that intrahypothalamic pre-
treatment with cyproheptadine or methysergide blocked apomor-
phine- or dopamine-induced hypothermia. They suggested that
a serotonin link existed in dopamine-receptor-mediated hypo-

thermia in the rat. In one study (Grabowska, 1974),
lesions of midbrain raphe prevented apomorphine-induced
hypothermia suggesting that the hypothermic action of apo-
morphine may be dependent upon activation of serotonin
neurons originating in the midbrain. A serotonergic link
has also been proposed in apomorphine-induced hyperthermia
in the rabbit (Quock and Horita, 1976). The antagonism of
apomorphine-induced hypothermia by cyproheptadine and
cinanserin support the theory of a serotonin link mediating
the thermal effects of apomorphine.

If serotonin activation must occur for apomorphine to
induce hypothermia in rats, it would be expected that
serotonin activation alone should induce hypothermia in rats.
Indeed, heat stress accelerates serotonin turnover in rat
brain (Chase and Murphy, 1973). Additionally, administra-
tion of 5-hydroxytryptophan with a peripheral decarboxylase
inhibitor produced hypothermia in rats (Grabowska et al.,
1973). This effect has also been demonstrated with trypto-
phan (Pawlowski, 1976), although cyproheptadine and methy-
sergide were shown to potentiate this effect -- an unexpected
finding. It was suggested that cyproheptadine and methyser-
gide do not block the serotonin receptors for which stimula-
tion leads to hypothermia. This brings up the possibility
of multiple receptors for both dopamine and serotonin in
producing hypothermia in rats. Since the serotonin antagon-
ists, cyproheptadine and cinanserin, potentiated lergotrile-
induced hypothermia while having the opposite effect on

apomorphine-induced hypothermia, it is suggested that apo-
morphine and lergotrile may act through different but parallel
dopaminergic pathways to produce hypothermia in the rat.

A recent body of evidence exists which suggests that
two or more distinct dopamine receptors exist. Two classes
of dopamine receptors have been defined according to their
association with, or independence from, dopamine-sensitive
adenyl cyclase (Kebabian, 1978; Schwarcz et al., 1978). It
has been proposed that those receptors unassociated with
adenyl cyclase be designated type alpha and those receptors
associated with adenyl cyclase be designated type beta
(Kebabian, 1978). Dopaminergic ergots such as lergotrile,
lisuride, and bromocryptine and specific antagonists such as
metoclopramide have been shown to be relatively specific for
the alpha-dopaminergic receptor in the anterior pituitary,
and fail to produce their effects upon the beta-dopaminergic
receptor in the striatum.

In view of the present findings, it appears that
serotonin may have a facilitatory role on beta-dopaminergic
receptor stimulation (by apomorphine) while antagonizing
alpha-dopaminergic receptor stimulation (by lergotrile). The
inability of parachlorophenylalanine to influence the change
in body temperature induced by apomorphine or lergotrile in
this study does not support this theory, but this lack of
significant results may be due in part to the effect para-
chlorophenylalanine itself had on the body temperature (see
Tables III and V).

The modification of dopaminergic-induced stereotypy by antiserotonin agents has received extensive investigation, but lacks agreement. This may be due to differences in evaluating the stereotypic behavior(s), the vast number of chemically different serotonin antagonists used, and differences between species studied. Several studies have reported the failure of serotonin agonists and antagonists to modify apomorphine-induced stereotypy in the rat (Rotrosen et al., 1972; Baldessarini et al., 1975; Calil et al., 1978). The present study is in agreement with another study that demonstrated reduction of apomorphine-induced stereotypy with the serotonin antagonists cyproheptadine and metergoline (Carter and Pycock, 1978). Still other studies report the potentiation of apomorphine-induced stereotypy by serotonin antagonists, indicating an inhibitory role for serotonin in this behavior (Weiner et al., 1975; Baldessarini and Griffith, 1976; Mogilnicka et al., 1977). These disagreements preclude the assignment of a single role for serotonin in apomorphine-induced stereotypy.

As with hypothermia, the antiserotonin effects on apomorphine-induced stereotypy were the opposite of the effects on lergotrile-induced stereotypy. This is a further indication that apomorphine and lergotrile do not stimulate identical dopaminergic pathways. This difference may involve the stimulation of adenyl cyclase-linked (beta type) dopamine receptors by apomorphine and stimulation of non-adenyl cyclase-linked (alpha type) dopamine receptors by lergotrile

to produce stereotypy in the rat. Another possible explanation is that apomorphine and lergotrile stimulate anatomically different dopamine receptor populations with differing serotonergic influence. Costall and Naylor (1975) have suggested that the tuberculum olfactorium and nucleus accumbens septi are more important in the low-intensity components (locomotion, sniffing) of stereotypy while the nucleus amygdaloideus centralis appears to be necessary for the high-intensity (gnawing, licking) components. In the present study, it was noted that lergotrile produced more mouth movements and less locomotion than apomorphine over the spectrum of doses used. Others have supported the stimulation of anatomically different receptors by apomorphine and lergotrile (Tye et al., 1977; Gianutsos and Moore, 1980). Additionally, much attention has focused on the presynaptic activity of dopamine agonists (Costall and Naylor, 1973a, 1973b; Silbergeld and Pfeiffer, 1977). Apomorphine has been reported to exert less presynaptic activity on dopaminergic neurons than bromocryptine or lergotrile (Silbergeld and Pfeiffer, 1977). It is unknown what influence serotonin may have on the presynaptic events of dopamine neurons, but if serotonin influences dopamine nerve cell firing, presynaptic actions of ergolines such as dopamine release or blockage of the reuptake of dopamine might be influenced by serotonergic manipulation.

The results of this study indicate that the dopamine agonists apomorphine and lergotrile do not produce their

similar effects through a common dopaminergic pathway. It may be possible that apomorphine and lergotrile activate two separate dopaminergic pathways, each with its own unique mode of serotonergic involvement. There is much evidence supporting this idea in the literature. Serotonin appears to play a facilitatory modulator role in the apomorphine-activated pathway, while serotonin seems to play an inhibitory modulator role in the lergotrile-activated pathway -- both pathways leading to outwardly identical effects of hypothermia and stereotypy.

It may be concluded from this investigation that (i) more than a single dopaminergic pathway is involved in producing hypothermia and stereotyped behavior in the rat; (ii) that these pathways are differentially affected by apomorphine and lergotrile; and (iii) that serotonin is intimately involved in both pathways, albeit in different manners.

Conclusions

The present study in male Wistar rats was designed to study the mechanisms of two effects (hypothermia and stereo-typed behavior) induced by the dopamine agonists apomorphine and lergotrile. It is generally accepted that these effects are produced in rats through central stimulation of dopamine receptors; however, several studies have indicated that serotonergic mechanisms may mediate or modify these "dopaminergic" effects.

The results of the present study demonstrate that differences exist as to the effects that known serotonin antagonists (cyproheptadine and cinanserin) have upon the hypothermic and stereotypic effects of apomorphine and lergotrile. Pretreatment with cyproheptadine had no effect upon apomorphine-induced hypothermia while it potentiated that of lergotrile. Moreover, pretreatment with cyproheptadine attenuated apomorphine-induced stereotypy while potentiating lergotrile-induced stereotypy. Pretreatment with cinanserin potentiated lergotrile-induced hypothermia and stereotypy while antagon-

izing both of these effects of apomorphine.

Parachlorophenylalanine effectively reduced whole brain serotonin content in rats, but failed to produce any significant change in the thermal response to apomorphine or lergotrile.

Haloperidol was found to antagonize both the hypothermia and stereotypy produced by apomorphine or lergotrile. This finding supports the dopaminergic nature of these effects.

The present findings suggest that serotonin plays a facilitatory modulator role in apomorphine-induced effects and that serotonin plays an inhibitory modulator role in lergotrile-induced effects. Recent studies by other investigators have suggested that two or more pharmacologically and anatomically distinct types of dopamine receptors exist. It would appear that apomorphine and lergotrile may have the ability to selectively stimulate these different dopamine receptor populations.

It may be concluded from this investigation that (i) more than a single dopaminergic pathway is involved in producing hypothermia and stereotyped behavior in the rat; (ii) that these pathways are differentially affected by apomorphine and lergotrile; and (iii) that serotonin is intimately involved in both pathways, albeit in different manners.

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