INFLUENCE OF SOME GABAergic AGENTS ON DRUG-INDUCED BEHAVIOUR IN CHICKS AND RATS.

BY

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DECLARATION

This is to certify that the work reported in this thesis was carried out by me in the Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, under the supervision of DR. E.N. SOKOMBA. The work of other investigators is acknowledged and referred to accordingly. I solemnly declare that no part of this thesis has been submitted elsewhere for a degree.

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DEDICATION

To my dear 'Bayo and our 'Dolapo, 'Bukola and 'Tope.

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ABBREVIATIONS :

ACH	-	Acetylcholine
ADR	-	Adrenaline
AMPHET	-	Amphetamine
AOAA	-	Aminooxyacetic acid
BBB	-	Blood-brain barrier
BIC	-	Bicuculine
CNS	-	Central Nervous System
DA	-	Dopamine
ECC	-	Excitation, chorea, circling
EEG	-	Electroencephalogram
EMG	-	Electromyogram
FLA-63	-	bis (1-methyl-4-homopiperazinyl thiocarbamate) disulphide
g	-	gramme
GABA	-	Gamma-aminobutyric acid
GABA-T	-	Gamma-aminobutyric acid-α-oxoglutarate transaminase
GAD	-	Glutamic acid decarboxylase
GHB	-	Gamma-hydroxybutyrate
hr.	-	hour
HS	-	Hyperstriatum
IDPN	-	$\beta'\beta'$-iminodipropionitrile
i.p.	-	Intraperitoneal
kg	-	Kilogramme
Mg	-	Milligramme
Mil	-	Millilitre
Min	-	Minute
Mm	-	Millimetre

NA	-	Noradrenaline
OT	-	Optic tectum
PIM	-	Pimozide
RES	-	Reserpine
RF	-	Reticular formation
sec	-	second
S.C.	-	Subcutaneous
THIP	-	4,5,6,7-tetrahydroisoxazolo-5,4-c-pyridin-3-ol
µV	-	Microvolt

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SUMMARY

The influence of some GABAergic agents on drug-induced stereotyped behaviour as a model of DA activation was studied in conscious young chicks.

Apomorphine and d-amphetamine produced dose-dependent stereotyped behaviour and d-amphetamine was observed to be less potent in producing this effect and in addition produced postural changes in the chicks.

Gama-aminobutyric acid (GABA), amino-oxyacetic acid (AOAA), gama-hydroxybutyrate (GHB) 4,5,6 7-tetrahydroisoxazolo 5,4-c-pyridin-3-ol (THIP) produced behavioural depression and sedation in chicks especially at lower doses while the GABA antagonist, bicuculine produced behavioural excitation,

Pretreatment of chicks with GABA, THIP, AOAA and GHB antagonized apomorphine and d-amphetamine-induced stereotyped behaviour while bicuculine potentiated the stereotypies induced by both drugs and also antagonized the effects of GABA, THIP and AOAA on apomorphine-induced stereotyped behaviour.

EEG studies using the GABAergic drugs on their own and in combination with the DA agonists substantiated the behavioural observations above.

Effect of some catecholaminergic agents on influence of GABAergic drugs on apomorphine and d-amphetamine-induced stereotyped behaviour were studied in chicks.

Reserpine potentiated apomorphine-incuced sterotyped behaviour while it antagonizes the effect of d-amphetamine. It also potentiated the effect of AOAA on d-amphetamine and antagonized the effect of AOAA and THIP on apormorphine-induced stereotyped behaviour,

Pimozide antagonized both apomorphine and d-amphetamine-induced stereotyped behaviour. It potentiated the inhibitory effect of GHB, AOAA and THIP on apomorphine,

FLA-63 antagonized apomorphine effect and potentiated d-amphetamine effect. FLA-63 potentiated the inhibitory effect of THIP and AOAA on apomorphine and antagonized effect of AOAA on d-amphetamine.

These results indicate that GABA exerts an inhibitory role over the DA system involved in inducing the stereotyped behaviour.

The behavioural effects of repeated doses of B'B'-iminodipropionitrite (IDPM) and the influence of GABAergic agents on the syndrome produced were studied in rats.

Repeated administration of IDPN (300 mg/kg for 7 days) induced distinct behavioural effects in rats characterized by excitation, choreiform head and neck movements and circling (i.e. ECC-syndrome).

Amphetamine potentiated both the circling and choreiform head and neck movements in the rats.

THIP. GHB and AOAA antagonized the ECC-Syndrome and also antagonized d-amphetamine-induced potentiation of the syndrome.

Bicuculine enhanced the syndrome and also potentiated (though insignificantly) the d-amphetamine effect on the syndrome.

These findings suggest that GABA may be involved in IDPN-induced hyperactivity in rats.

CHAPTER 1

LITERATURE REVIEW

1.1 Introduction

Early studies have indicated that gamma-amino butyric acid (GABA) is the major inhibitory transmitter in the central nervous system especially in the grey matter (Florey, 1957, Neal and Iversen; 1971). Regional distribution of GABA and other putative neurotransmitters and their enzymes have indicated that in all species, the level of GABA was highest in the substantia nigra and globus pallidus, although the hypothalamus and caudate nucleus also have high concentrations (Fahn and Coté, 1968; Okada et al, 1971). The activity of GABA synthesizing enzyme, glutamic acid decarboxylase (GAD) was also high in these areas (Lowe et al, 1958; Fahn and Coté, 1968).

Dopamine (DA) too is predominant in the basal ganglia especially the striatum and the regional distribution also parallels that of its synthesizing enzyme (dopa decarboxylase). The fact that GABA is found in high concentrations in DA containing striatal and limbic regions suggests a functional inter-relationship between these two transmitter systems. In fact, the ascending nigro-striatal pathway has been suggested to be dopaminergic where DA serves as an excitatory transmitter (Andén et al, 1964; Poirier et al, 1965) while the descending striato-nigral and pallido-nigral pathways are GABAergic with

GABA serving as an inhibitory transmitter (Riese, 1924; Okada, 1976). Thus, it was thought for a considerably long time that dopaminergic activity is directly and tonically regulated by a GABAergic striato-nigral or striato-pallido-nigral feedback loop.

Recent results however disagree with this hypothesis (Scheel-Kruger et al, 1977, 1978; Christensen et al, 1978). For example, systemically administered muscimol, a GABA receptor stimulating agent(Enna and Snyder, 1977), inhibited neuronal activity more effectively in pars reticulata of the substantia nigra than in pars compacta and these reticulata cells are also more sensitive to iontophoressed GABA than the nigral DA cells (Aghajanian and Bunney, 1974). Furthermore, muscimol has been observed to increase DA synthesis and firing rates of DA cells. Drugs that increase GABA levels have also been observed to have little effect on tonic DA activity. Whatever the reasons for the discrepancy between these recent results and those predicted by striato-nigral feedback model, these studies point at difficulty in predicting behavioural effect that will dominate after systemic injections of GABAergic drugs administered alone, in low or high doses or in combination with other drugs influencing the monoamine system.

1.2 Gamma-amino butyric acid (GABA)

GABA was for many years known as a product

of microbial and plant metabolism (Ackerman, 1910; Stewart et al, 1949). It was identified in mammalian brain by Roberts, Harmann and Frankel, (1950) and Roberts and Frankel, (1950). About the same time, GABA was identified in the brain tissues of the mouse, rat, guinea-pig, rabbit, turtle, chicks etc. (Underfiend, 1950; Awarapa et al, 1950). In vertebrates, GABA is confined to the central nervous system whereas in invertebrates, it is also found in the peripheral nervous system (Roberts et al, 1950; Otsuka et al, 1967).

1.2.1 Distribution

The regional distribution of GABA in mammalian brain has been described by many authors (Baxter and Roberts, 1959; Okada et al, 1971). In all species, specifically high amount of GABA was found in the substantia nigra, globus pallidus and other extrapyramidal structures such as putamen and caudatus. High concentrations were also observed in the hypothalamus, superior colliculus, nucleus oculomotoris and nucleus dendatus while much lower levels were found in whole cerebral hemisphere, the pons, the medulla and white matter of the spinal cord.

A remarkably high activity of glutamic acid decarboxylase (GAD), was reported in all the areas having high levels of GABA (Albers and Brady, 1959; Fahn and Coté, 1968). This high level of GABA may thus reflect high GAD activity. The amount of GABA present at anytime in a particular area of the CNS is probably a reflection of the balance between the

rate of formation and the rate of utilization. Several findings have suggested that GABA does not cross the blood-brain barrier (BBB) readily and as such systemic administration of GABA does not elevate brain GABA level appreciably (Van-Gelder and Elliot, 1958; Purpura et al, 1976). However, physiologically disturbed or diseased areas of brain might allow passage into cerebral tissue of blood-borne GABA due to altered blood-brain barrier (Purpura et al, 1958).

1.2.2. Synthesis of GABA

GABA is formed in the brain to a large extent from L-glutamic acid by the action of L-glutamic acid decarboxylase (GAD), an enzyme thought previously to be found only in CNS almost entirely in the grey matter (Roberts, 1956).

$HOOCCH_2CH_2CH(NH_2)\ COOH$

L-glutamic acid

GAD

+

Vit. B_6 (Co-enzyme)

$HOOC\ CH_2CH_2CH_2{}^3NH_2\ +\ CO_2$

GABA

With recent improvements in analytical methods, it was discovered that GAD can also be found in non-neuronal tissues e.g. heart, blood vessels, liver, kidney and does not cross-react with the GAD in neuronal tissue (Zachmann et al. 1966; Kuriyama et al. 1970). The decarboxylation reaction is

essentially irreversible and proceeds anaerobically and this accounts for the rapid elevation of GABA levels in conditions of anoxia (Thorn et al. 1973) including changes which occur in brain soon after death unless the tissue is quickly frozen. GAD has an optimum pH of about 6.5, and requires pyridoxine (Vit. B6) as a co-enzyme (Tower, 1956; Roberts, 1974). Thus, under normal condition GAD might be the rate limiting reaction of the GABA sequence.

1.2.3 Metabolism of GABA

GABA-α-ketoglutarate transaminase shortened as GABA-transaminase (GABA-T) is found in the CNS also chiefly in the grey matter though exists in other tissues (Bessman et al, 1953; Roberts and Brogoff, 1953).

GABA-T catalyses the reversible transamination of GABA with α-ketoglutarate.

$$HOOCCH_2CH_2CH_2NH_2 + HOOC\ CH_2CH_2C^{O}\ -COOH$$

GABA α-ketoglutaric acid

$$\underset{\text{Vit. B6}}{\overset{\text{GABA-T}}{\rightleftharpoons}}\ HOOC\ CH_2CH_2CHO + HOOC\ CH_2CH_2(NH_2)\text{-}COOH$$

Succinic semi-aldehyde L-glutaminic acid

GABA-T has an optimum pH of 8.2, requires full oxygenation and also pyridoxine which it is capable of storing as a co-factor because it is more tightly bound to it than it is to GAD thus it is not very sensitive to pyridoxine deprivation (Baxter and Roberts, 1958). L-glutamic acid is a by-product of the reaction but to date there is no evidence.

suggesting formation of significant amounts of GABA by reactions other than that catalysed by GAD.

GABA can also undergo various other transformations in the CNS apart from transamination and subsequently entering the Kreb's cycle though these pathways are believed to be of little qualitative importance (Baxter, 1976). The brain also contains a dehydrogenase which catalyses the rapid irreversible oxidation of succinic semi-aldehyde to succinic acid (Albers & Salvador, 1958) which in turn can be oxidized via the reactions of tricarboxylic acid cycle.

$$HOOC\ CH_2CH_2CHO + DPN + H_2O$$

SSA ↓ SSA dehydrogenase

$$HOCCH_2CH_2COOH + DPNH + H+$$

succinic acid

1.2.4 Role of GABA in CNS

GABA was first identified as a normal constituent of brain tissues in 1950 (Awarapa et al, 1950; Roberts and Frankel, 1950). Some years later, some workers Hayashi (1956), Hayashi and Nagai (1956) found that GABA has an inhibitory effect on the electrical activity of the vertebrate nervous system. Most of the investigations analyzing the mechanism of GABA's depressive action on CNS have been conducted on spinal motor neurones.

On cerebral cortex and cerebellum, GABA has been shown to have a strong inhibitory action (Fahn, 1976) very much identical to synaptic

inhibition (Curtis and Watkins, 1960; Krnjević, 1976) which is the principal form of inhibition in the brain. Thus, it inhibits cell firing and also produces fall in resistance and hyper-polarization with a reversed potential that is practically identical to the inhibtory post-synaptic potential. This potential leads to a reduction in excitability and depression of excitatory post-synaptic potentials (EPSPS) independently of previous activity. The changes, as observed by these workers, are brought about by GABA causing increased permeability to chloride ion (Cl^-) whose equilibrium potential is at least 10 mV more negative than the resting potential.

Also, direct application of GABA on crayfish stretch-receptor (Kuffler and Edwards, 1958) and electrophoretic application of GABA onto spinal interneurones and neurones of the cerebral cortex (Boistell and Fatt, 1958) were found to produce marked depressant action on the firing rate of these neurones.

Furthermore, in all mammalian species, GABA has been found to be formed and located almost entirely in grey matter which contains areas associated with inhibitory function (Fahn and Coté, 1968; Okada et al, 1971).

Lastly, the relationship between GAD inhibition and seizure inductions has shown that

convulsions can be produced either by inhibition of enzymatic activity of GAD which is responsible for GABA synthesis (Robert and Frankel, 1950) or by compounds like allylglycine, hydrazines and thiosemicarbazide and genetically determined or nutritionally produced Vit. B_6 defficiency (Bain and Williams, 1960; Killam, 1957). The seizures produced can be prevented by prior topical or i/v administration of GABA (Killam, 1957; Killam et al, 1960) and also by administration of Vit. B_6 which is an essential co-factor for all cerebral decarboxylases and transaminases. So far in general, it can be said that the effect of GABA on mammalian CNS are inhibitory and hyperpolarizing.

De Groat, (1970) and De Groat et al, (1971 and 1972) studied some ganglia (superior cervical, inferior mesenteric, pelvic nodose and lumbar dorsal root ganglia) of the cat and rabbit in situ and observed depolarizing or excitatory effect of GABA. This observation was supported by those of Browery and Brown, (1974) and Nishi et al, (1974). In every instance, this depolarization was found to be one-third that of ganglionic cholinergic agonists (Ach and carbachol). In addition, the depolarization was blocked by GABA antagonists (bicuculline and picrotoxin) in low concentrations. Further work on ionic mechanism of GABA action on bull dog dorsal root ganglia by Nishi et al,(1974) showed that the equilibrium potential for depolarization was linearly related to the log of external

chloride concentration. It was therefore concluded that the depolarization caused by GABA is due to an increased chloride permeability. Thus, chloride permeability is a common target for GABA action and the resultant effect would then depend on the intracellular chloride concentration of each cell (Woodward et al, 1969).

1.2.6 GABA Agonists.

Several findings have suggested that parenteral administration of GABA does not cross blood-brain barrier readily (Roberts et al, 1958; Van Gelder and Elliot, 1958; Purpura et al, 1958). Thus there arose the need to find structural analogues of GABA able to cross blood-brain barrier or some other ways by which GABA levels may be increased if the need arises.

(a) Muscimol (3-hydroxy-5-aminomethylisoxazide)

It is a structural analogue of GABA (Brehm et al, 1972). It was characterized and proposed as a GABA agonist by Enna and Snyder in 1977. It depresses firing of central neurones (Curtis et al, 1971; Krogsgaard-Larsen et al 1975). It also inhibits neuronal (Johnston, 1971) and glial (Schousboe et al, 1978) uptake processes by being a substrate for neuronal transport carrier. However, it is a relatively toxic compound (Biggio et al, 1977), a property either inherent to muscimol or due to its conversion to toxic metabolites in vivo (Krogsgaard-Larsen and Arnt, 1978).

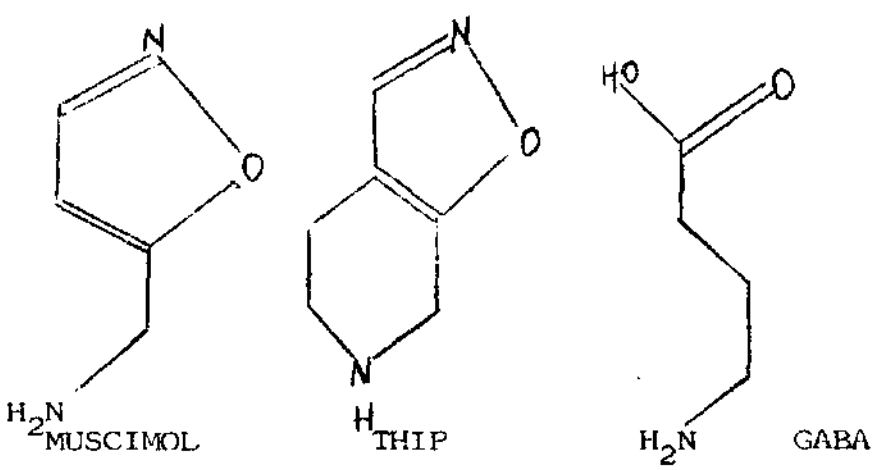
Thus muscimol may not be a potentially useful drug. However, in view of its dual effects on GABA system, it serves as a model compound for the development of both specific uptake inhibitors and GABA receptor agonist. There is abundant evidence to show that the structure of muscimol is optimum for binding to GABA receptors and of all the putative agonists available to date (that cross blood-brain barrier), it has the greatest affinity for the GABA receptor (Krogsgaard-Larsen and Arnt, 1978; Browery et al, 1980). Muscimol also has a facilitating influence on the DA systems, increasing DA synthesis and firing rates of DA cells, indicating that there may exist at least 2 types of GABA receptors in the brain, one which may be inhibitory to ascending DA system and the other type which may be excitatory to DA systems. Behavioural studies have indicated that the excitatory effects may prevail over inhibitory ones particularly under conditions whereby increased DA receptor activity already exists (Delini-Stula, 1979).

(b) THIP (4,5,6,7-tetrahydroisoxazolo-5-4-c-pyridin-3-ol).

THIP is a specific and potent GABA receptor agonist without any influence on GABA uptake, GABA metabolising enzyme and on other neurotransmitter systems.

THIP is not as potent and toxic as muscimol. When administered in vitro or in vivo , THIP does

not stimulate benzodiazepine binding sites quite unlike GABA and muscimol suggesting that THIP may be a useful therapeutic agent in certain clinical disorders, e.g. Huntington's chorea and schizoprenia. In such disorders, enhancement of GABA mediated transmission is required as it may selectively interact at one type of GABA site in brain. (WasZczak et al. 1980).



(c) GHB (Gamma-hydroxybutyrate).

GHB is also a structural analogue of GABA which is capable of crossing blood-brain barrier. It causes sedation in man and other mammalian species (Laborit et al, 1960; Jouany et al, 1960 a and b). GHB has been suggested to act probably by formation of GABA (Basil et al, 1964; Fishbein and Bessman, 1964). GABA undergoes transamination in brain to succinic semialdehyde after which it is converted to GHB by a specific dehydrogenase. Intraperitoneal injection of GHB has been shown to increase brain levels of GABA (Sisken et al, 1961). It also has the ability to inhibit unit activity in the substantia nigra (Pericic et al, 1978).

In addition, GHB has an interesting inter-relationship with the catecholamines, in that in doses which produce sedation, it produces a selective increase in brain DA concentration in brain areas associated with high DA content (Aghajanian and Roth, 1970). This is because it inhibits impulse flow in DA neurons in the substantia nigra zona compacta, sending their axon to the striatum. GHB is also reported to block DA release by nerve endings thus explaining both the DA accumulation and CNS depression produced by GHB (Gessa et al, 1966). Its mechanism of impulse flow inhibition is not yet clear but it has been suggested that it acts synergistically with the action of inhibitory GABAergic nerve terminals in substantia nigra (Andén et al, 1978).

(d) AOAA((Aminooxyacetic acid)

AOAA is a potent GABA-T inhibitor with consequent increase in GABA levels (Wallach, 1961; Baxter and Roberts, 1961; Kuriyama et al, 1966).

AOAA has been shown to have a convulsant (Da Vanzo et al, 1961; De La Mora and Massien, 1969) and anticonvulsant (Da Vanzo et al. 1961; Kuriyama et al, 1966) action in rats and mice depending on the amount administered and whether it affects GABA metabolism or not (Wallach, 1961; Baxter and Roberts, 1961). There is also variation in response to anticonvulsant action of AOAA depending on the nature of the convulsant

agent used, After electroshock, the anticonvulsant effect was observed at 1.5 hours and absent at 6 hours (Kuriyama et al, 1966) whereas with metrazole and thiosemicarbazide (Kuriyama and Da Vanzo, 1961), the anticonvulsant effect was observed at both pretreatment times but considerably less at 6 hours than at 1.5 hours while protection was of similar magnitude with isoniazid as the convulsant agent. This might reflect the involvement of 2 different mechanisms in the action of AOAA, a fast developing but short lasting effect not involving GABA metabolism and a slow developing and long lasting effect involving GABA metabolism (Wood and Peesker, 1973).

In low doses, AOAA behaves as a potent GABA-T inhibitor with antiepileptic effect in chicks (Osuide, 1972), rats and mice (Wood and Peesker, 1972 a and b). However, at high doses, AOAA inhibits GAD thus inhibiting GABA formation and sensitizing the animal to epileptogenic stimuli (Wallach, 1961; Osuide, 1972).

Other GABA-T inhibitors are hydroxylamine, hydrazine and gamma-acetylinic GABA. They are all less potent than AOAA with hydroxylamine being the least potent (Wood and Peesker, 1975).

1.2.7 GABA Antagonists

No specific GABA receptor antagonist is available at present that has a greater affinity for the receptor than GABA itself (Olsen, 1976).

(a) Bicuculline (BIC)

It is a convulsant alkaloid. It is a fairly potent and specific GABA antagonist (Curtis et al, 1971; Johnston, 1976). Because of its structural similarity to GABA, it was thought that it might be a competitive inhibitor of GABA at receptor in vertebrates (Johnston, 1976; Mohler and Okada, 1977). In addition, it produces a rapid and reversible antagonism of depressant action of GABA (McLennan, 1976b) but it has been observed to produce non-competitive inhibition of GABA responses in invertebrates (Shank et al, 1974; Takuechi, 1976). Furthermore, it has been observed to block GABA-induced membrane conductance (Takuechi and Onodera, 1972) suggesting that it probably acts on the ionophore that is regulated by GABA receptor rather than the receptor itself. Some other workers have found no effect of BIC (bicuculine) on some GABA synapses in vertebrates (Godfrain et al, 1970; Straughan et al, 1971) and invertebrates (Earl and Large, 1974; Swagel et al, 1974). This conflicting report is probably due to its low solubility as when administered iontophoretically, the amount delivered may bear little relationship to the ejecting current due to its low transport number in the pipette and when given intravenously its action will not be restricted to one specific brain area. This difficulty, added to anatomical complexity of the cerebral cortex, probably accounts for the difference of opinion in

the use of bicuculine as a GABA antagonist.

Other effects of BIC are inhibition of acetylcholinesterase (Svenneby and Roberts, 1976), potentiation of acetylocholine action (Muller and McLennan, 1974) and direct modification of nerve axon or muscle membrane (Freeman, 1973).

(b) Picrotoxin

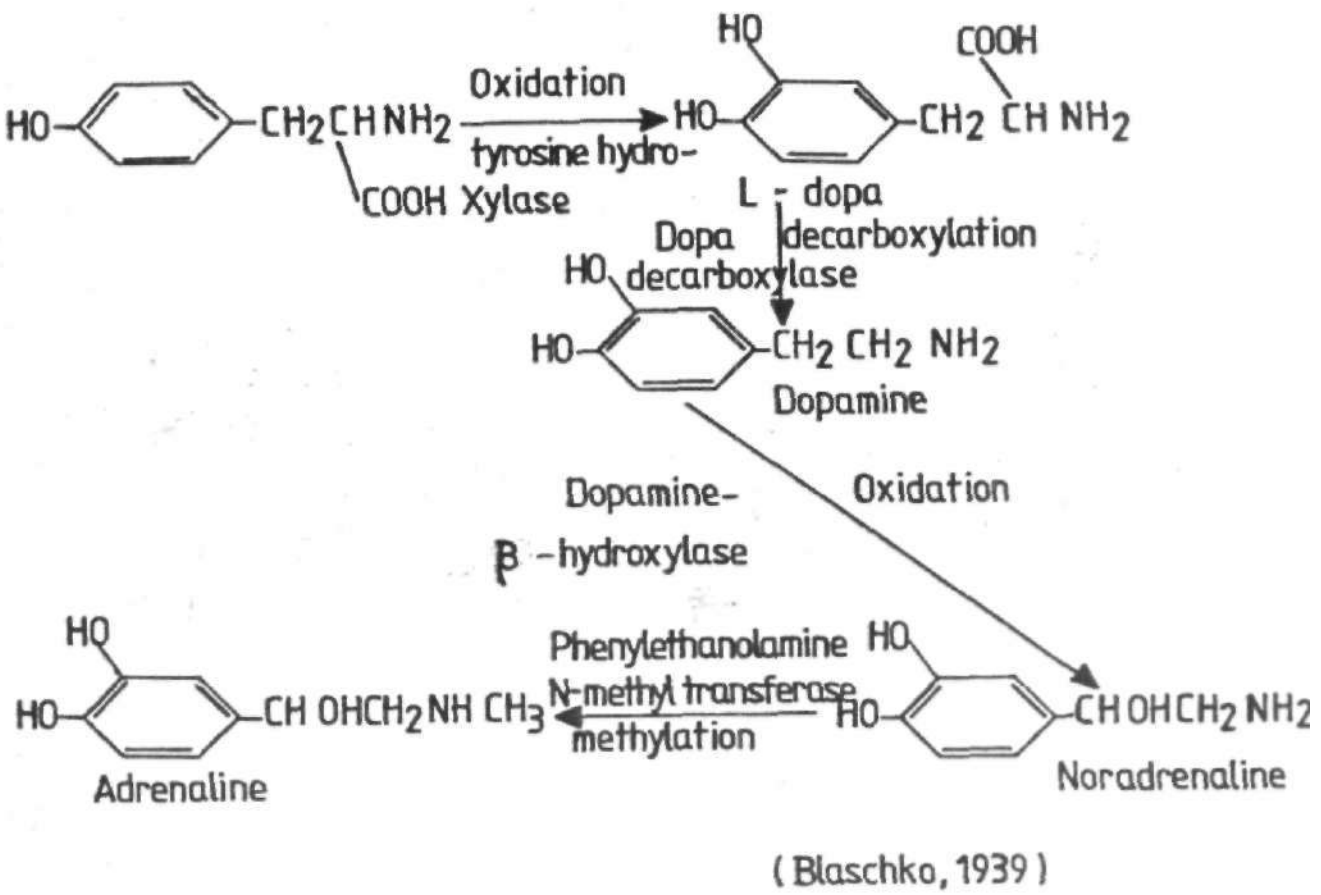
Picrotoxin specifically blocks GABAergic synapses and this blocking action is well documented (Grundfest, et al, 1959; Takuechi and Takuechi, 1969; McLenan, 1973). Like bicuculine, it also affects the muscle membrane conductance directly (Grundfest et al, 1959; Shank et al, 1974) and its inhibition is strictly non-competitive (Nishi et al, 1974).

1.3 Dopamine

Discovery of noradrenaline (NA) synthetic pathway revealed the existence of DA which was for a long time thought to serve a percursor role only (Blaschko, 1959; Nagatsu, 1964). Later, it was found that the concentration of DA in some areas of brain are proportional to those of NA (Andén et al, 1964) while in some areas of brain e.g. caudate nucleus with high DA concentration, NA concentration is extremely low which suggest a transmitter role for DA. Finally the implication of DA and not NA in the pathophysiology of Parkinson's disease has established DA as a transmitter in its own right.

1.3.1 Synthesis of DA

DA and other naturally occuring catecholamines are synthesized in sympathetic adrenergic neurones in adrenal medulla and other chromaffin tissues and in brain from amino acid percursor L-tyrosine by a series of enzymatic reactions (Blaschko, 1939; Nagatsu, 1964).



(Blaschko, 1939)

Main pathway in the synthesis of catecholamine.

L-tyrosine is present in the body in form of protein and is taken up from the blood stream by an active mechanism to be concentrated in adrenergic neurones and brain. The first enzymatic reaction in the synthetic pathway, catalyzed by tyrosine hydroxylase which requires oxygen and ferrous iron radical tetrahydroheptadine is the slowest and thus the rate limiting step in the synthesis of catecholamines (Nagatsu et al, 1964).

1.3.2 Inactivation of DA

Enzymatic degradation is the main process by which DA is inactivated. The two principal enzymes involved are monoamine oxidase (MAO) and catechol-O-methyl-transferase (COMT) (Blaschko et al, 1937; Axelrod, 1959).

After release, DA is first acted upon by MAO rapidly to form 3,4,dihydroxyphenylacetic acid (DOPAC) which is then o-methylated to give Homovanilic acid (HVA) or 4-hydroxy-3-methoxy-phenylacetic acid as the main metabolite (Carlsson and Hillarp, 1962).

1.3.3 Physiological role of DA

Biochemical, electrophysiological and pharmacological approaches have been used to study the physiological role and clinical significance of DA in mammals (Andén et al, 1964; Van Rossum, 1967; Connor, 1968). DA acts both centrally and peripherally. Its peripheral effects are similar

to those of NA and adrenaline (ADR) but relatively weaker and is partly due to direct action on the receptor and partly to release of catecholamine from adrenergic neurones (Berger and Dale, 1910; Holtz et al, 1939). Centrally, DA was first thought to serve percursor role only but workers like Carlsson (1959), Hornykiewicz (1966), have accumulated evidence showing that DA has a transmitter role. This is supported most convincingly by the fact that concentrations of DA in certain regions of mammalian brain are extremely high (e.g. caudate nucleus, globus pallidus and substantia nigra) while that of NA is extremely low. They also observed decrease in DA concentration in corpus striatum of Parkinson's disease patients indicating pathophysiological role for brain DA in psychomotor function (Fog and Pakkenberg, 1970; Randrup and Munkvad, 1972).

A great deal of research had been carried out on the influence of catecholamine in various behavioural patterns. For example, Godwin et al, (1970) have shown that administration of dihydroxyphenylalanine (DOPA, the immediate percursor of DA) elicited both behavioural and locomotor activation with accompanying EEG arousal while Mandel and Spooner (1968) observed sedation after administration of NA into the brain of various experiemental animals thus giving support to the speculation by Everett and Weigard (1962) that DA and not NA is the principal catecholamine subserving arousal state

function. Further experiments led to the suggestion that DA and NA mediate different behavioural patterns, the NA system being associated with gross spontaneous activity while the DA system was associated with stereotyped behaviour (Randrup and Jonas, 1967). These workers also suggested that stereotyped behaviour and locomotor activation induced by amphetamine may be related to increased DA and NA concentrations respectively.

1.4 Drug-induced stereotyped behaviour.

This has been defined as a perseverative, continuous and apparently aimless activity during which there is absence of normal behaviour (Randrup and Munkvad, 1966). The characteristic feature of the pattern that emerges depends on the animal species with variation even within the same species and the type and dose of drug (Molander and Randrup, 1974). Thus, there is a continuous twitter movements and pecking in chicks (Osuide and Adejoh, 1973) and pigeons (Dhawan and Saxena, 1960) while with rats, mice and guinea pigs, there is continuous biting, sniffing and licking (Schelknov, 1964; Randrup and Munkvad, 1966).

Several studies on stereotyped behaviour have implicated brain dopaminergic system as the mediator of this behaviour. Lesion studies have implicated specifically those of extrapyramidal areas i.e. the nigrostriatal DA system.

Chemical lesions of the substantia nigra

abolished the stereotypic behaviour while lesions of NA pathway were without effect, (Asher and Aghajanian, 1974; Creese and Iversen, 1972, 1974). Electrolytic lesion of the caudate nucleus, putamen and globus pallidus (Naylor and Olley, 1972) and injection of low doses of haloperidol antagonized the stereotypy (Pijnenburg, 1973). Most of the drugs that produce stereotyped behaviour affect this dopaminergic system either directly or indirectly or both. They may either increase the release of DA or act as DA receptor agonists.

Amphetamine has been reported to act indirectly by releasing catecholamines and inhibiting their uptake (Ungerstedt, 1971; Randrup and Munkvad, 1966). In addition, it inhibits the activity of monoamine oxidase enzyme. (Besson et al, 1971; Clarke, 1980).

Amantadine is believed to act indirectly by causing the release of DA from extragranular store in dopaminergic neurons (Farnebo et al, 1971) and also block DA neuronal uptake while L-dopa produces its central actions by being converted to DA in the brain (Bartholini and Pletscher, 1968).

Apomorphine, piribedil and ergometrine have been reported by many workers to act directly on DA receptors (Corrodi et al, 1973; Ernst, 1967).

Other neurotransmitters also play a role in stereotyped behaviour e.g. acetylcholine has

been reported to antagonize apomorphine-induced stereotyped behaviour (Arnfred and Randrup, 1968; Osuide and Adejoh, 1973).

Noradrenaline (NA) which peripherally is more active on α-receptors than on β -receptors has been observed by some workers not to have any effect on drug-induced stereotyped behaviour (Randrup and Scheel-Kruger, 1966; Hollister et al, 1974) while other workers have observed an inhibitory influence of central adrenergic mechanism on drug-induced stereotyped behaviour (Mogilnicka and Braestrup, 1976).

Role of serotonin (5-HT) however is not very clear whereas some workers have reported data suggestive of an inhibitory action of 5-HT on drug-induced stereotyped behaviour (Weiner et al, 1973 and Saxena et al, 1977), others have reported attenuation (Costall and Naylor, 1974b). A third group of workers did not observe any effect (Randrup and Munkvad, 1966; Breese et al, 1974).

1.5 Interaction between GABA and DA

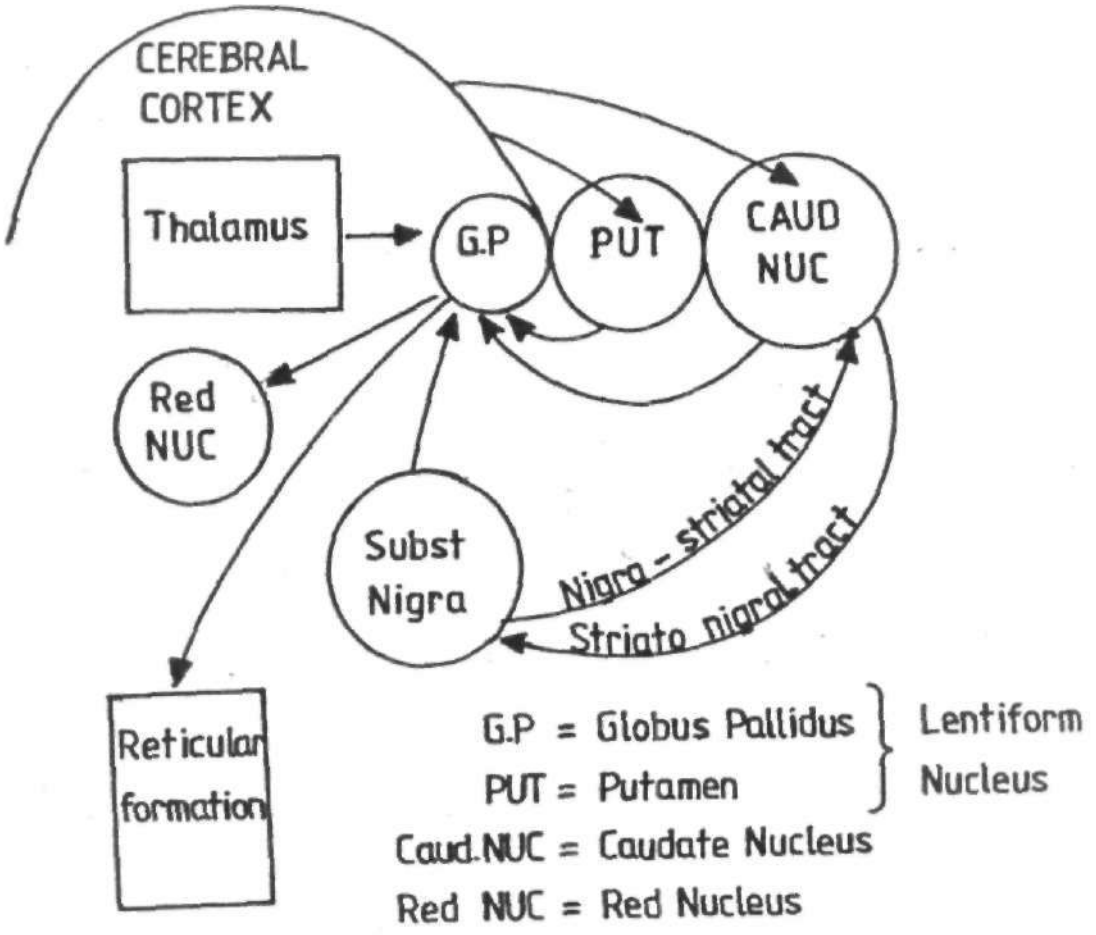
Relative to NA, it is widely documented that there is very high concentration of DA in the corpus striatum, the globus pallidus and the substantia nigra (Carlsson, 1959; Ehringer and Hornykiewicz, 1960).

The same fact holds for GABA and GAD which show particularly high concentrations in globus pallidus and substantia nigra of all species (Fahn, 1976).

A large number of nigral GABA nerve terminals probably make axodendritic contact with DA dendrites in the substantia nigra (Roberts et al, 1960). There is also evidence of a rich network of GABA terminals making axodendritic and axosomatic contacts with the nerve cells present within the medial forebrain bundle area and with dendrites extending into the islands of Calleja and into parts of the cell body layer of olfactory tubercle. Thus, GABAergic mechanisms possibly exist beyond the DA receptors since the outer layer of this structure at least partly project into the deeper structure like islands of Calleja. Therefore, GABA receptors here may block or enhance the effect of post-synaptic DA receptor activity.

Furthermore, there exists within globus pallidus a dense GABAergic innervation which form baskets around the large multipolar cells of this nucleus. Since the efferent outflow to a large extent passes via the globus pallidus, thalamus and hypothalamus to reach the motor cortex, GABAergic mechanism could predictably modify the influence of post-synaptic DA receptor activity. Finally, the organization of the striatonigral pathway doesn't support the hypothesis of a simple feedback system directed towards the DA cells (Tulloch et al, 1978)

Most of the research findings prior to 1978 lent support to the concept that the ascending nigrostriatal pathway was DA-ergic with DA serving as an excitatory transmitter (Andén et al, 1964; Poirier et al, 1974) while the descending striatonigral pathway is GABAergic with GABA subserving an inhibitory role (Vogt, 1937; and Okada, 1976).



It had also been observed that GABA locally controls the release of DA from nerve terminals by intrinsic striatal interneurones (Stoof and Mulder, 1977). It could therefore be expected that the consequences of DA deficiency or excess would be modified by GABA action on DAergic pathways, within the basal ganglia and vice-versa in both striatal and mesolimbic areas (Fuxe et al, 1976; Costall et al, 1976).

Behaviourally, it was also thought that specific GABA neurone agonists (e.g. THIP and Muscimol) are inhibitory to DA neurones (Tarsy et al, 1975). Furthermore, it had been shown that elevation of cerebral GABA levels is associated

with akinesia while blockade of central GABA function produces hyperactivity, myoclonic jerks and general seizure (Pycock et al. 1976).

Also GABA mimetic drugs had been shown to significantly potentiate the catalepsy produced by neuroleptics (Kaarianen, 1976; Worms and Lloyd, 1978). Focal injection of GABA bilaterally into nucleus accumbens inhibited both the hyperactivity induced by injection of DA into this site and the increased locomotor effect of systemically administered amphetamine (Kaarianen, 1976).

The interaction between GABA and DA systems are infact more complex and less predictable than would appear hitherto. They may inhibit or potentiate each other. For instance, in one study, muscimol significantly reduced apomorphine-induced stereotypy (Fuxe et al, 1976). In another study, muscimol and other GABA agonists facilitated the intensity and occurrence of stereotyped gnawing but simultaneously depressed the locomotor activity produced by DA stimulants (Scheel-Kruger et al, 1978). Also, local injection of muscimol into the substantia nigra induces central stimulation in rats (Scheel-Kruger et al, 1977; Arnt and Scheel-Kruger, 1979). This central stimulation has been found to be completely independent of DA activity (Arnt and Scheel-Kruger, 1980) because stimulation persisted and infact was intensified after DA. depletion. The inhibitory effects of these GABA mimetics have also been found to be partially

antagonized by bicuculline. These findings are certainly not consistent with the traditional hypothesis that GABA within substantia nigra only inhibited DA-neuronal activity.

Single-unit activity studies show that muscimol inhibited neuronal activity more effectively in the pars reticulata of the substantia nigra than in pars compacta. This finding is also consistent with the observation that the reticulata cells are more sensitive to iontophoresed GABA than the nigral DA cells (Eng and Walter, 1980; Afghan and Bunney, 1974) thus the sensitivity of the reticulata cells may parallel a normal sensitizing of these cells to endogenously released GABA. These pars reticulata cells can also be considered possible sites of termination of the striato-nigral GABA pathway. All these could be explained on the basis of the recent anatomical concept described above (Tulloch et al, 1978).

Muscimol also produced an increase in DA turnover in agreement with the work of Biggio et al (1977) who reported increases of homovannilic acid levels following muscimol administration. The effect is preferentially located in the motor centres, caudate nucleus and nucleus accumbens and disappears at highest doses whereas GABA-T inhibitor reduces DA turnover. This is because in this dose range, muscimol preferentially activates certain types of GABA receptors (muscimol-sensitive GABA receptors) located perhaps

beyond the DA receptors and to a lesser degree activates the DA dendrites of the substantia nigra. It could thus elicit compensatory increase of DA turnover. Disappearance of the effect at high doses is probably due to activation of GABA receptors in the substantia nigra and Area 10 which sends DA fibres to the mesolimbic region thus having an inhibitory influence on DA neurons.

Finally, it has been noted that GABA mimetic drugs (except AOAA) attenuate the increase in DA synthesis following treatment with haloperidol (Andén, 1974; Keller et al, 1976). AOAA on the other hand, produced a decrease in DAergic activity after haloperidol treatment (Walters et al, 1976).

It could be summarized therefore that these inconsistencies are probably due to the fact that the striatonigral feedback loop affect the DA neurons indirectly through nigral interneurones or via local dendroaxonal and axo-dendritic interactions (Raabi et al, 1977). Thus, if several GABA synapses are involved in the feedback loop, it would be difficult to predict how GABA mimetics would modify DAergic activity. In this light, GABA agonist might also produce complex spectrum of effects if besides interacting with post-synaptic GABA receptors, they preferentially inhibit GABA neurons and/or interact with GABA neurons on DA terminals.

1.6 Clinical Implication of the Interaction.

Studies on brains of deceased Parkinson and Huntington's chorea patients have indicated an imbalance between GABA and DA in these diseased states. In schizophrenia, it has been discovered that there's decreased GABA activity in certain brain regions of schizophrenic patients (Roberts, 1974; Van Kammen, 1977).

1.6.1 Parkinson's Disease

In this disease, GAD has been shown to be reduced to 20-50% of normal in striatum, globus pallidus and substantia nigra while (^{3}H) GABA binding is normal in striatum, globus pallidus and decreased in substantia nigra (Bird and Iversen, 1974; Lloyd et al, 1975). Thus GABA in both striatum and globus pallidus might be involved in the restoration of DA function which is the practical problem but that of substantia nigra is unlikely to be influenced as the nigral cell themselves are lost. Lloyd and Hornykiewicz (1973) demonstrated that this reduced GAD content in all structures returned to normal after prolonged L-Dopa therapy i.e. there is reversible functional reduction in GABA activity. A drug that selectively inhibits GABA synthesis or its post-synaptic action may be beneficial in Parkinson's disease but in view of the apparent inhibitory effect of GABA on nigral DA neurons, an agent which selectively inhibits GABA action in nigral might drive the remaining nigral

neurons to produce as much DA as possible (Bernheimer et al, 1973; Hornykiewicz et al, 1976).

1.6.2 Huntington's Chorea

In this condition, remarkable decreases in GABA levels (Perry et al, 1973) and GAD activities (Bird and Iversen, 1974; McGeer et al, 1973) have been found in the striatum (including accumbens), pallidum and substantia nigra. In effect, the theoretical aim would be to increase GABA action in the striatum, substantia nigra and globus pallidus by using a directly acting GABA agonist specific to these sites. Similarly, a directly acting GABA agonist acting on substantia nigra would decrease nigro-striatal dopaminergic activity. Finally, GABA stimulation in globus pallidus should provoke a decrease in dyskinetic phenomena as it produces an akinetic-rigid syndrome (Marsden, 1977). Thus, a directly acting GABA agonist affecting all these three sites would provide the ideal therapy in Huntington's chorea.

1.6.3 Schizophrenia

Current data suggest that the defect in this condition may not lie in the function of DA neurons themselves but rather in their activity relative to other neuronal system e.g. GABA in which it is the weak component (Roberts, 1972). Bird et al (1977) reported a significant loss of post-mortem GAD activity in several brain regions in psychosis.

In addition to the use of anti-psychotic drugs, some methods may be devised in which the potencies or firing rates of GABA could be enhanced thus correcting the imbalance between the two systems.

Initial attempts to manipulate GABA action employing GABA itself and GABA mimetic drugs in basal ganglia diseases have been uniformly unsuccessful in patients with Parkinson's disease (Barbeau, 1973; Taminga, 1978) and Huntington's chorea (Fisher et al, 1974; Paulson, 1976) except in the study by Bartholini et al, (1979) where the symptoms were reduced in patients having the disease for less than 4 years. In schizophrenia, preliminary clinical studies showed an enhancement of the symptoms but reduction of tardive dyskinesia (Taminga et al, 1978b; Kobayashi, 1977; Chase and Taminga, 1979).

This is probably not because the concepts are wrong but the tools available have not been adequate. Furthermore, the wide distribution of GABA in the brain provides a basis for adverse effect at one site and beneficial effects at another, quite apart from the unwanted effect it may produce elsewhere in the basal ganglia.

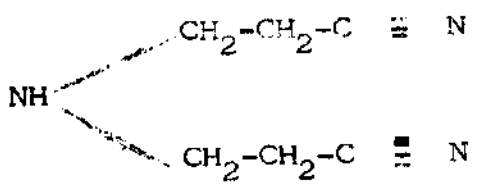
However, following various animal models of GABA action in different regions of the basal ganglia for site selective action of GABA by Marsden (1978) in conjunction with regional biochemical studies, there was great hope of development of rational drug therapy aimed at

correcting specific GABA abnormalities in diseases of basal ganglia.

This new horizon was opened by studies with THIP (Sytinsky et al, 1978) which is less toxic than the GABA agonist (muscimol) formerly in use thus well tolerated.

1.7 Excitement, Chorea and Circling Behaviour (ECC-syndrome)

Administration of β'β'-iminodipropionitrile (IDPN) to rats and mice has been observed to produce a variety of neurological symptoms (Delay et al, 1952; Selye, 1957). It has been shown to elicit a hyperkinetic syndrome characterized by excitation with fine tremors, choreiform head and neck movements and circling which led to the syndrome being called ECC-syndrome (Selye, 1957).



IDPN

Other abnormalities produced by IDPN in rats are kyphosis, ataxia, paresis of the hindlimbs, a tendency towards retropulsion, inability to swim (Gabay, 1966) and blindness (Forgacs, 1966). Similar responses have been observed using chlorinated tertiary amines, (Goldin et al, 1948) hexose reductase, (Cutting et al, 1960) and arsinilic acid (Selye et al, 1972). Other substances structurally similar to IDPN like B'-iminodipropionitrile (Schilling and Strong, 1954) and

methyleneaminoacetonitrile (Gabay et al, 1961) have also been observed in experimental animals to produce gross skeletal deformities with connective tissue abnormalities in toxic doses and that pretreatment with thyroxine protected the animals against these toxic effects (Schilling and Strong, 1954; Gabay et al, 1961).

Following research on the underlying causes of this ECC-syndrome, Hartman et al (1968) have described histological lesions occuring in many areas of the central nervous system of IDPN-treated animals with a swelling of the proximal segment of axons (Chou and Hartmann, 1964).

Histochemical and biochemical analysis of these axonal balloons have detected an increase in axoplasmic protein content with no apparent change in RNA content (Diezel and Ule, 1963). Various biochemical determinations on whole brain tissue have been carried out and these include measurement of free amino-acids (Vivanco et al, 1966), GABA and GABA transaminase activity (Gabay 1966), aromatic aminotransferase activity (Gabay and Huang, 1959), adenine nucleotides (Williams et al, 1968) and overall metabolism (Brownlow and Heath, 1969). Further neurochemical and pharmacological studies have implicated 5-HT and DA in IDPN's behavioural effects (Langlais et al, 1965; Gabay et al, 1974). Similar observations have been made by Sokomba and Osuide (1983) in

chicks. These workers indicated a role for DA and 5-HT in this syndrome and an inhibitory role for cholinergic system.

However, in spite of all these studies, the primary anatomical and neurochemical basis for this syndrome is yet to be elucidated. The similarity between the features of the "ECC-syndrome" and certain human hyperkinetic disorders has led some workers to suggest that the syndrome could be used as an animal model of such disorders (Langlais et al, 1975).

1.8 Aims and objectives of this project.

A. Behavioural effect of GABA and its interaction with DA agonists in young chicks.

Behaviourally, GABA and GABA-mimetic drugs were thought to be inhibitory to DA (Tarsy et al, 1975; Fuxe et al, 1976). However, recent results have shown that the interaction between GABA and DA system are more complex and less predictable than previously thought (Scheel-Kruger et al, 1977a; Olianas et al, 1978 and Arnt and Scheel-Kruger, 1979). In some models, GABA agonists potentiated or mediated dopaminergic effects while in other models, they antagonized the effects of DA thus indicating difficulty at predicting behavioural effects of systemically administered GABAergic drugs given alone or in combination with drugs affecting monoaminergic system.

In the light of these inconsistencies, the objective of this project is to study the behavioural and electroencephalographic effects of some GABAergic drugs alone and in combination with DA agonists in conscious young chicks and to compare the results with those that have been reported in other species bearing in mind both concepts of GABA-DA interaction.

B. Excitement, Chorea and Circling Behaviour (ECC-syndrome).

β'β-iminodipropionitrile (IDPN) has been shown to elicit a permanent hyperkinetic syndrome characterized by excitation with fine tremors, choreiform head and neck movements and circling whick led to the syndrome being called ECC-syndrome (Selye, 19 7). Several biochemical and pharmacological studies have been carried out in IDPN-treated animals and have indicated a role for 5-HT, DA and cholinergic systems in this syndrome (Langlais et al, 1975; Gabay et al, 1974; Sokomba and Osuide, 1983). In spite of these, the primary underlying causes of the syndrome still remain unknown. The objective of this part of the project is to study the influence of some GABAergic drugs in IDPN-induced behavioural syndrome in rats with a view to elucidating the role of GABA in this syndrome. Furthermore, GABA has been shown to interact with other neurotransmitters especially DA in the central nervous system. It is intended to study the effect of interaction between GABA and DA in this syndrome.

CHAPTER 2

MATERIALS AND METHODS

2.1 Experimental Animals

White ranger cockrels (warren strain) 2-5 days old weighing between 30 and 50 grammes obtained locally from Arewa Agricultural Enterprisee Ltd, Zaria and albino rats (inbred in the Faculty animal house) weighing 95-150 grammes were used for this project.

2.2. Drug Solutions.

(a) Preparation of Drug solution: Apomorphine hydrochloride (British Drug Houses Ltd.) solution was prepared by dissolving the powder in boiled distilled water and kept in an amber coloured air-tight bottle. 0.1% w/w sodium metabisulphite was added to the weighed quantity of apomorphine hydrochloride before the preparation of each solution to enhance stability since apomorphine hydrochloride solution decomposes readily when exposed to air or light. A fresh solution was prepared for each day's experiments.

(b) Both bicuculine (Sigma Chemical Co. Ltd) and pimozide (Janssen Pharmaceutica) were suspended in 3% V/V Tween 80 and adjusted to the appropriate volume with normal saline.

(c) FLA-63 (Regis Chemical Co.) was dissolved in 0.05M HCL with the aid of gentle heating over a water bath and appropriate dilutions were made with normal saline.

(d) Reserpine (Ciba) was supplied in ampoules and appropriate dilutions were made with normal saline.

(e) β'β'-iminodipropionitrile hydrochloride (IDPN, Eastmann Kodak) was prepared daily by dissolving the crystals in phosphate buffer, pH7.0.

(f) Solutions of THIP (H. Lundbeck Co. A/S), d-amphetamine Sulphate (Smith-kline and French Laboratories), GABA (Koch Light), Amino-oxyacetic acid (Sigma Chemical Co.) GHB Na Salt (Sigma Chemical Co.), were prepared with normal saline. Fresh solutions were prepared for each day's experiment.

2.3 Routes of Administration

Apomorphine and AOAA were administered subcutaneously while all the other drugs were administered intraperitoneally.

2.4 Controls

The control animals were administered with the vehicles used in preparing the drug solutions.

2.5 Stereotyped Behavioural Studies using young chicks.

Chicks of the same age and approximately

the same weight were observed in pairs in a clean cage for 1-1½ hours in a quiet room. The chicks were provided with food and water throughout the experiment.

Using two hand tally counters, one in each hand with the help of a trained assistant, 4 behavioural parameters were counted and these are, chick pecking at its own foot, pecking at the other chick's body and foot without pulling it, pecking at non-food objects and fighting episodes.

For each day's experiment, 5 pairs of chicks were used with the first and last pairs serving as controls in which only the DA agonist (apomorphine or d-amphetamine) was injected and the first control experiment was followed by 3 consecutive ones in which the chicks were pretreated with the GABAergic drug before administration of DA agonist. The behavioural effects of the GABAergic agents were also studied.

2.6 Implantation of Electrocortical and Electromyograph Electrodes

Each chick was anaesthetised with halothane (May and Baker Ltd.) and the head was held firmly in a stereotaxic instrument. The scalp was exposed and the head was levelled using a spirit level. Co-ordinates were taken using the bregma as the zero point. The chicks were implanted with electrodes made from the pointed ends of stainless steel insect pins No. 00 according to the method of Spooner (1965) as modified by Osuide (1972).

Monopolar electrodes were implanted into the hyperstriatum (HS) and optic tectum (OT) while bipolar electrodes were implanted into the pontine reticular formation (RF). These brain areas were implanted using the following co-ordinates:-

HS: anterior-posterior, + 3.8 mm. lateral, -3.4 mm;

OT: anterior-posterior, - 2.4 mm. lateral, -5.9 mm;

RF: anterior-posterior, - 2.0 mm. lateral, r+ 1.5 mm. Vertical, -8.1 mm. Electromyograph (EMG) electrodes, also made with stainless steel pins but bent at the end to make hooks were inserted into the left semispinalis capitis muscle of one side of the dorsolateral aspect of the neck. A similar electrode was inserted into the comb to serve as a reference electrode for the monopolar electrodes. All these electrodes were chronically secured in position with dental cement powder and fluid. After the implantation process, the chicks were kept warm using angle-poised lamp and allowed 24 hours for full recovery from halothane before EEG recording.

2.7 EEG Recording.

The chick was placed in a screened cage and allowed 1 hour to settle down in the new environment before EEG recording. The recording of both EEG and EMG were carried out on Grass Polygraph, Model 79D. The electrodes from the chicks were connected to the terminals of the polygraph using amphenol connectors (Part No. 2211 No. 7) and recordings from the hyperstriatum and optic tectum

were taken using the comb as the reference.

2.8 ECC-Syndromized Rats.

White albino rats were used for this study. The rats were injected daily with IDPN (300 mg/kg base) for seven days. The ECC-syndrome appeared on the 7th day and the rats were allowed one week to regain their weights and for the syndrome to stabilize before they were used for drug studies.

In the case of single drug study, control observations were carried out for 1 hour before the rats were treated with the drug to be tested. After drug treatment, observations were continued for another 1 hour during which the choreiform head and neck movements and circling were recorded using hand tally counters.

2.9 Statistical Method.

A programmable calculator Texas model (TI 58) was used for the statistical calculations using the following formula for student's t-test.

$$\frac{X - Y}{\sqrt{\frac{1}{n_1} + {}^{1}/_{n_2}} \times \sqrt{\frac{(S_1)^2 x(n-1) + (S_2)^2 x (n-2)}{(n_1-1)+(n_2-1)}}}$$

X = mean of total pecking activities in the control group.

Y = mean of total pecking activities in the drug-treated group.

n_1 = number of pairs of chicks in the control group.

n_2 = number of pairs of chicks in the drug-treated group.

Mean and Standard deviation were calculated by using standard programme given by the manufacturer of the calculator.

Standard Error of Mean is

$$\frac{S.D.}{\sqrt{N}}$$

S.D. = Standard deviation.

N = number of pairs of chicks.

Same statistical calculation was used for the readings obtained from the rat experiments.

CHAPTER 3

RESULTS

3.1 Apomorphine: (0.02-0.5 mg/kg)

Apomorphine produced a dose-dependent behavioural excitation in young chicks. Low doses (0.05 mg/kg) and below produced intermittent chirping in the chicks.

However, high doses (0.1-0.2 mg/kg) induced distinct behavioural excitatory effects in the chicks while with doses above 0.2 mg/kg. the hyperactive behaviour was so intense that accurate counting was almost impossible. The hyperactive state was characterized by loud chirping and rapid movements inside the cage. There were also fighting episodes in which a chick grasped at the other's foot until the chick fell or sometimes there may be frontal attacks in which one chick pecked the other in the region of the beak and the eye. Most of the time, the fighting episodes were so intense that the feet and beak bled but this did not prevent further pecking at the same spot. Generally, during the attack, no one chick was dominant. The hyperactive state usually started 5-10 minutes after drug administration and continued for 25-30 mins. This state was usually followed by a state of depressed activity in the chicks: the chicks remaining calm or sedated. However, few chicks had persistent excitatory behaviour. The sum of the four parameters recorded was taken as the degree of abnormal behaviour (Table I).

Drugs	Dose (mg/kg)	Mean of total activity recorded ± S.D.
Saline	0.2 ml.	106.67 ± 28.0
APOM	0.05	263.0 ± 35.0
	0.10	766.67 ± 75.8**
	0.20	1558.33 ±186.4*
	0.40	2685.25 ±275.3*
AMPHET	1.0	153.50 ± 32.0
	2.5	238.67 ± 53.0**
	5.0	659.87 ± 65.5*
	10.0	916.17 ± 92.7*

TABLE I: Effect of various doses of apomorphine and d-amphetamine on pecking activities in chicks, * and ** are significantly different from saline controls and represent $P < 0.001$ and $P < 0.005$, Student's t -test
S.D. = Standard deviation
n = 6 pairs per dose.

D-amphetamine (0.02-10 mg/kg)

Like apomorphine, d-amphetamine produced a dose-dependent behavioural excitation. Low doses (0.02-0.25 mg/kg) did not produce any observable change in the behaviour of the chick.

0.5-2.5 mg/kg produced slight behavioural excitation. Higher doses of 5 mg and above induced distinct stereotyped pecking activity and postural changes in the chicks, characterized by chirping, spreading of the wings, sitting on the metatarsus with the trunk against the floor of the cage with continuous twittering (high toned, rapidly repeated sounds) and usually appearing 8-15 mins. after administration of the drug. The stereotyped behaviour was similar to those of apomorphine but less intensive and the fighting episodes were mostly restricted to frontal attacks.
D-amphetamine effects persisted longer than those induced by apomorphine (Table I). Thus, observations were carried out for 1½ hours for d-amphetamine experiments and 1 hour for apomorphine experiments.

3.2 GABA (20mg - 500mg/kg)

Doses of GABA below 50 mg/kg did not produce observable change in the behaviour of the chicks.

Dose of 100-200 mg/kg produced slight behavioural depression in the chicks. With 250-500 mg/kg, chicks appeared sedated with initial behavioural excitation lasting for about 10 mins. (Table II).

Drugs	Dose (mg/kg)	Mean of total activity recorded ± S.D.
Saline	0.2 ml	175.33 ± 55.8
GABA	50	205.17 ± 62.5
	100	95.33 ± 35.7***
	250	50.20 ± 22.8**
	500	15.67 ± 5.3*
GHB	10	160.50 ± 45.3
	25	120.33 ± 38.9
	50	75.50 ± 26.7**
	100	40.83 ± 18.3**
	250	28.00 ± 10.3*
THIP	0.05	163.42 ± 55.3
	0.10	110.33 ± 36.0
	0.25	72.50 ± 30.3**
	0.50	40.92 ± 22.8**
	1.00	19.75 ± 8.3*
AOAA	0.5	180.75 ± 48.5
	1.0	160.85 ± 40.0
	2.5	80.00 ± 25.7**
	5.0	41.33 ± 18.8**
	8.5	12.75 ± 6.5*
BIC	0.5	160.33 ± 66.7
	1.0	198.65 ± 67.8
	2.5	402.38 ± 75.3**
	5.0	667.25 ± 79.7*
	10.0	738.67 ± 83.3*

TABLE II: Effect of various doses of GABAergic agents on pecking activities in chicks
*, ** and *** are significantly different from saline controls and represent $P < 0.001$, $P < 0.005$ and $P < 0.05$, student's t - test
S.D = Standard deviation.
n = 6 pairs per histogram.

GABA (100 mg/kg) administered 15 mins previously antagonized apomorphine (0.125 mg/kg) P 0.005 and d-amphetamine (5 mg/kg)-induced stereotyped behaviour ($P < 0.005$) (Fig. 3.1).

THIP (0.05-5 mg/kg)

0.05-0.5 mg/kg of THIP slightly sedated the chicks while higher doses (0.5-5 mg/kg) produced greater sedation (Table II).

THIP (0.2 mg/kg) administered 15 mins prior to administration of apomorphine and d-amphetamine antagonized the stereotypy induced by these drugs ($P < 0.001$ and $P < 0.005$ respectively) (Fig. 3.2).

AOAA (0.5-10 mg/kg)

With doses below 2 mg/kg there was no observable change in the behaviour of the chicks.

2.5-5 mg/kg produced signs of slight CNS depression with the chicks looking drowsy and inactive. 6-8 mg/kg of AOAA gave rise to a state of behavioural excitation characterized by loud chirping and later clonic convulsions (Table II). Higher doses (8.5-10 mg/kg) produced clonic/tonic convulsions in the chicks and occasionally death. AOAA (2.5 mg/kg) administered 1 hour previously antagonized both apomorphine and d-amphetamine-induced stereotypies ($P < 0.001$) (Fig. 3.3).

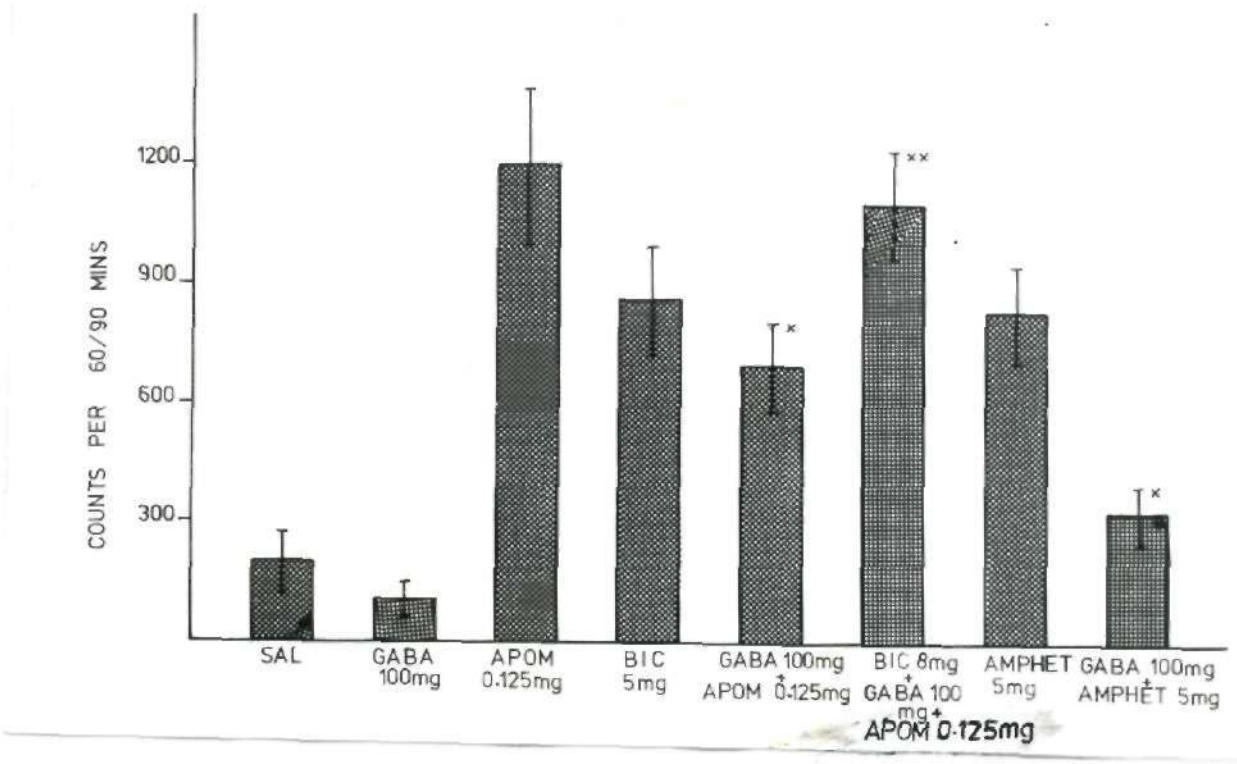


Fig. 3.1 Effect of GABA and its interaction with bicuculine on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Pretreatment time for GABA and bicuculine was 15 mins. Each histogram is the mean of total activity recorded. Vertical bars indicate standard deviation.
* and ** are significantly different from saline controls and corresponding drug controls and represents $P < 0.005$ and $P < 0.05$, student's t - test ($n = 6$ pairs per histogram).

Saline (ml)	APOM (mg/kg)	THIP (mg/kg)	AOAA (mg/kg)	Mean of total activity recorded ± S.D.
0.2	-	-	-	130.67 ± 45.0
-	0.125	-	-	1074.00 ± 107.7
-	0.125	0.1	-	811.67 ± 81.5
-	0.125	0.2	-	572.52 ± 57.8*
-	0.125	0.5	-	364.33 ± 28.1*
-	0.125	1.0	-	154.84 ± 20.7*
-	0.125	-	0.5	920.33 ± 95.6
-	0.125	-	1.0	708.00 ± 68.3
-	0.125	-	2.5	473.67 ± 48.3*
-	0.125	-	5.0	113.25 ± 18.6*

TABLE III: Effect of various doses of THIP and AOAA on apomorphine-induced stereotyped behaviour in young chicks. Pretreatment time for THIP and AOAA were 15 mins and 1 hr. respectively.
* is significantly different from saline controls and corresponding drug controls and represents $P < 0.001$, student's t - test.
S.D = Standard deviation.
(n = 6 pairs per dose).

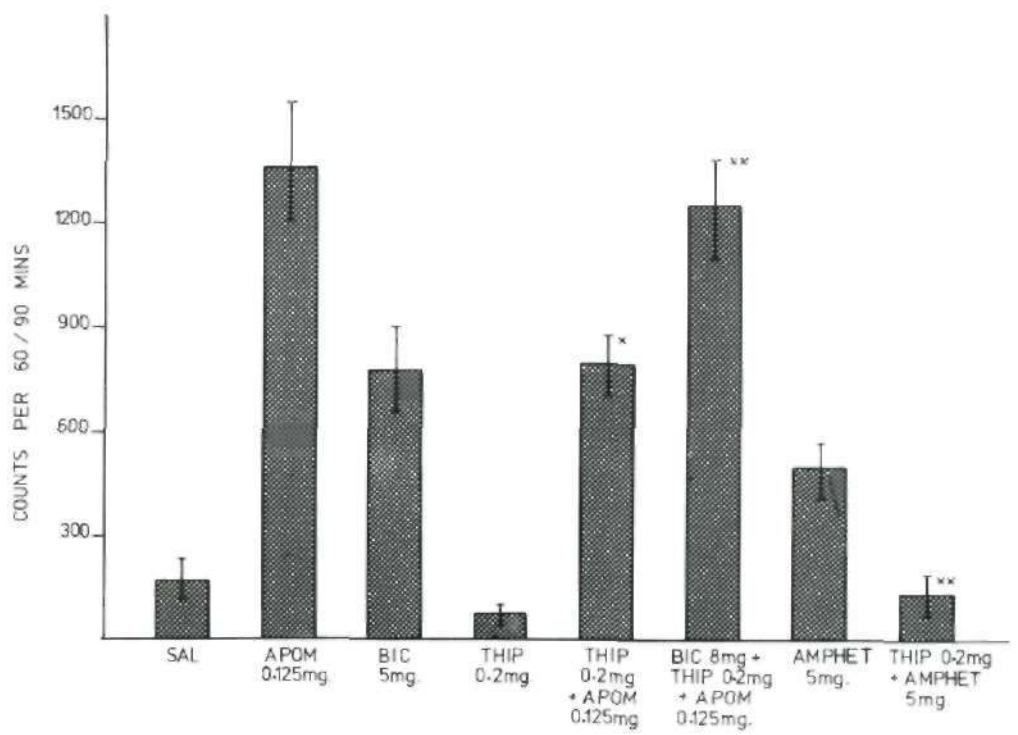


Fig. 3.2 Effect of THIP and its interaction with bicuculine on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Pretreatment time was 15 mins. Each histogram is the mean of the total activity recorded. Vertical bars indicate standard deviation. * and ** are significantly different from saline controls and corresponding drug controls and represent $P < 0.001$ and $P < 0.005$, student's t - test. (n = 6 pairs per histogram).

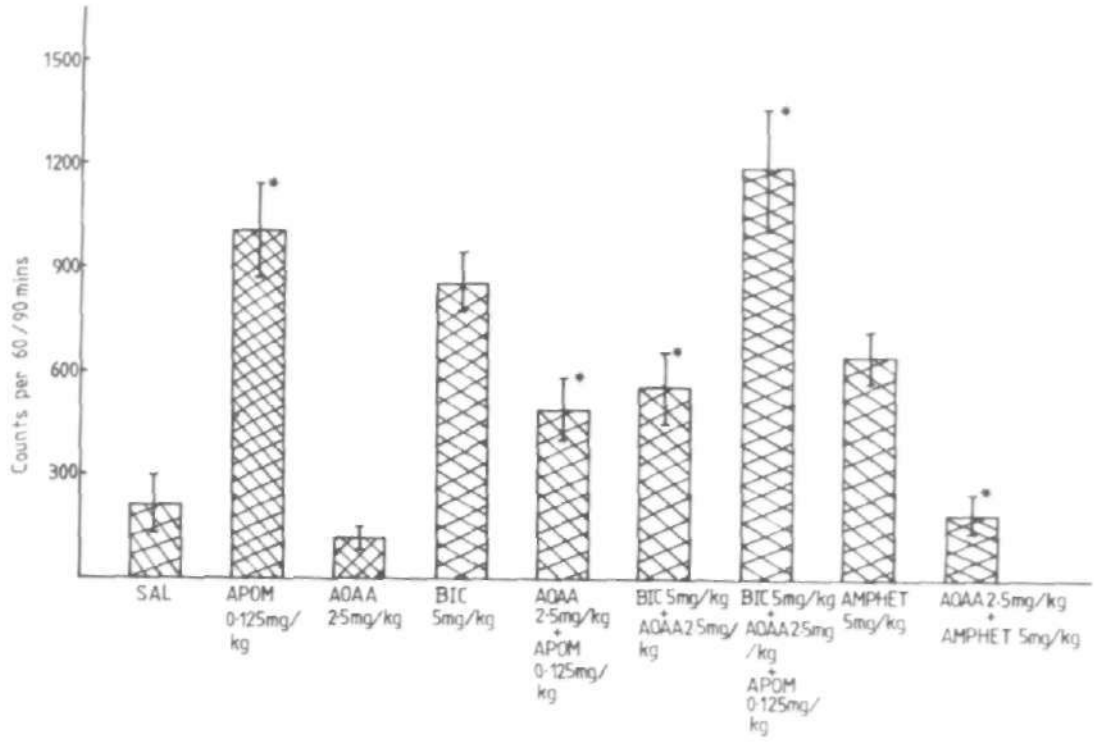


Fig. 3.3 Effect of AOAA and its interactions with bicuculine on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Pretreatment time for bicuculine was 15 mins. and 1 hr. for AOAA. Each histogram is the mean of total activity recorded. Vertical bars indicate standard deviation. * is significantly different from the saline and corresponding drug controls and represents $P < 0.001$, student's t - test. (n = 6 pairs per histogram).

GHB (5 mg - 1 g/kg)

Doses below 20 mg/kg produced no observable change in the behaviour of the chicks. With 20-100 mg/kg. the chicks appeared slightly drowsy but easily aroused.

150-250 mg/kg produced sedation within 15 mins and lasting for some 40 mins after which pecking activity resumed intermittently (Table II) 1 g/kg produced clonic convulsions about 10 mins after administration of drug.

GHB (50 mg/kg) administered 1 hour prior to apomorphine and d-amphetamine antagonized the stereotyped behaviour induced by these drugs ($P \leq 0.005$ and $P < 0.05$ respectively). (Fig. 3.4).

Bicuculine (BIC) (0.5-20 mg/kg)

Doses of BIC below 1 mg/kg produced no change in normal behaviour of the chicks, while doses of 2.5-10 mg/kg produced behavioural excitation with loud chirping and several attempts at jumping out of the cage. Pecking activity was on and off and lasted throughout the period of observation. At any given time, the pecking activity was more than normal and mainly restricted to pecking at non-food objects. They were however, less intensive than with apomorphine and d-amphetamine.(Table II).

15-20 mg/kg produced clonic and sometimes tonic convulsions. BIC (5 mg/kg) when given 15 mins prior to administration of apomorphine or amphetamine

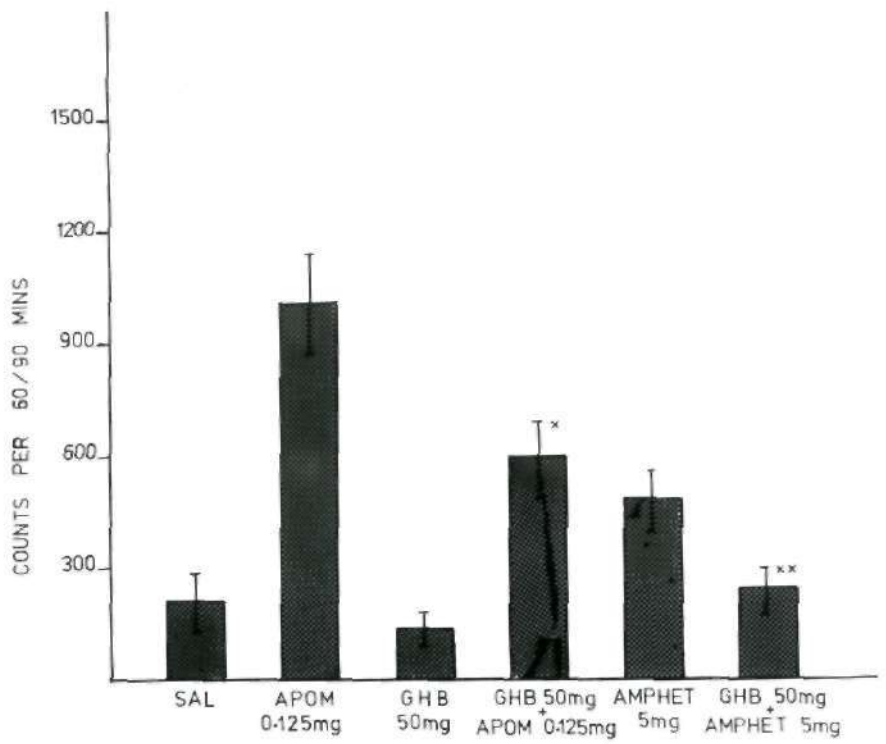


Fig. 3.4 Effect of gamma-hydroxybutyric acid (GHB) on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Pretreatment time was 1 hour. Each histogram is the mean of total activity recorded. Vertical bars indicate standard deviation. * and ** are significantly different from the drug controls and represent $P < 0.005$ and $P < 0.05$, student's t - test. (n = 6 pairs per histogram).

in the chicks, potentiated the stereotypies induced by either drug ($P < 0.05$). (Fig. 3.5)

Bicuculine antagonized the inhibitory effect of AOAA, THIP and GABA on apomorphine-induced stereotyped behaviour.

3.3 EEG Result.

(a) With normal saline, EEG activity was slow in all the areas studied, the chicks were usually calm and chirped intermittently.

(b) Apomorphine at 15 mins, desynchronized the waves in the HS, OT and RF though the RF was least affected and the EMG was slightly activated. The EEG was characterized by low amplitude high frequency waves. (Fig. 3.6).

(c) D-amphetamine showed desynchronization in all the areas studied accompanied with increase in EMG activity (Fig. 3.6)

(d) GABA at 15 mins produced slight synchronization of the waves in the HS and OT while RF and EMG were not markedly affected. At 60 mins there was distinct synchronization in HS, OT and RF and decrease in EMG activity (Fig. 3.7). GABA administered 15 mins prior to apomorphine produced synchronization of the waves in HS, OT without much effect on RF but the EMG activity was increased. Thus GABA antagonized the desynchronization effect of apomorphine in HS and OT. With D-amphetamine, prior administration of GABA

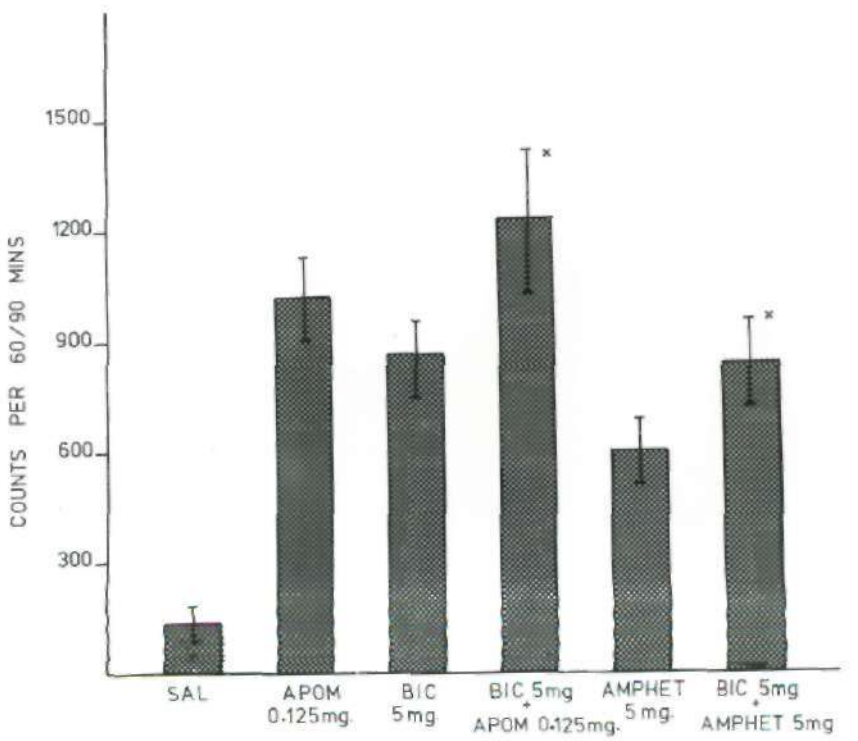


Fig. 3.5 Effect of bicuculine (BIC) on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Pretreatment time was 15 mins. Each histogram is the mean of total activity recorded. Vertical bars indicated standard deviation. * is significantly different from the drug controls and represent $P < 0.05$, student's t - test. (n = 6 pairs per histogram).

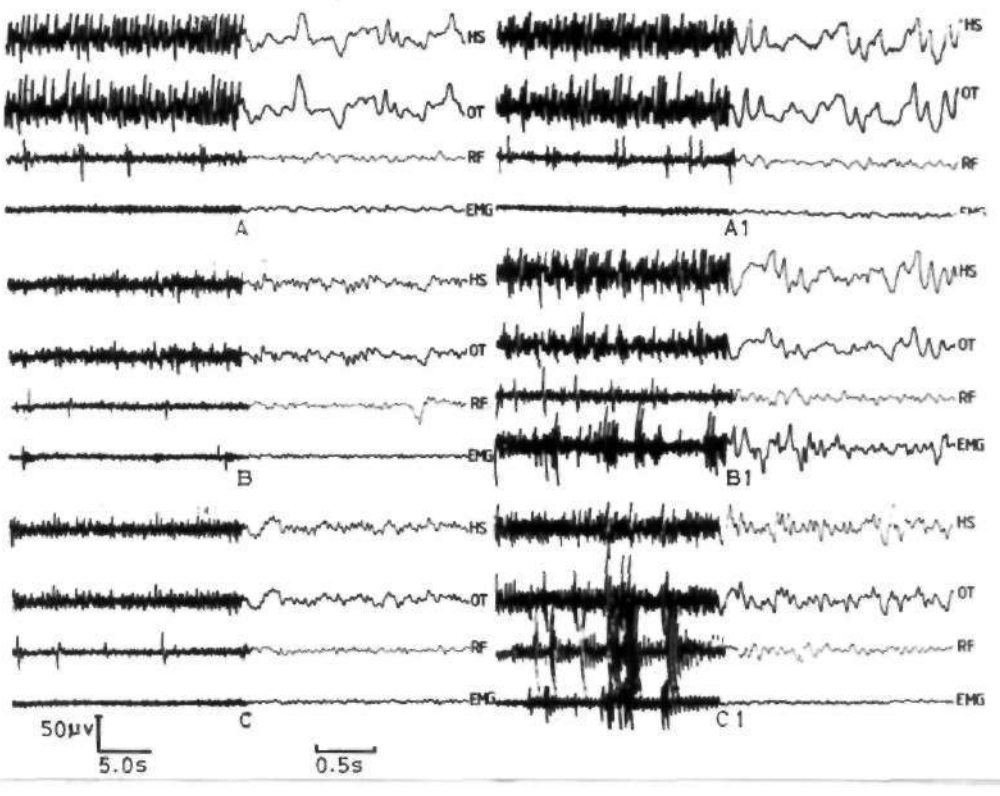


Fig. 3.6 Effects of apomorphine (0.125 mg/kg) and d-amphetamine (5 mg/kg) on the EEG activity in young chicks.
A/A_1 were saline controls
B/C^1 were the effects of APOM at 15 min. and 30 min post injection.
B_1/C_1 were the effects of D-AMPHET at 30 min. and 60 min. post injection.

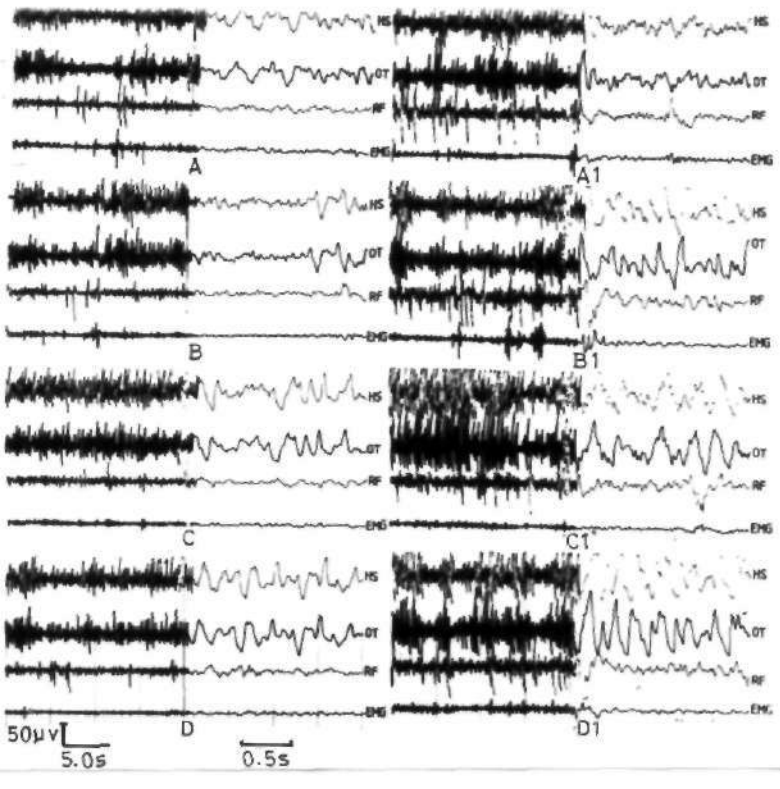


Fig. 3.7 Effects of GABA (100 mg/kg) and THIP (0.20 mg/kg) on the EEG activity in young chicks.
A/A_1 were saline controls
B/B_1 were the effects of GABA/THIP at 15 mins.
C/C_1 were the effects of GABA/THIP at 30 mins.
D/D_1 were the effects of GABA/THIP at 60 mins. post injection respectively.

produced synchronization of the waves, in HS, OT and RF with an accompanied decrease in EMG activity. Thus GABA antagonized the effect of d-amphetamine in all the areas studied (Fig. 3.8).

(e) THIP synchronized the waves in the HS, OT and slightly in the RF without significant effect on EMG activity. (Fig. 3.7). It also synchronized the waves in the HS, OT and RF when administered 15 mins prior to apomorphine but the EMG activity was increased. THIP antagonized the desynchronization produced by d-amphetamine in the HS, OT and RF by synchronizing the waves in these areas but the EMG activity was increased. These results indicate antagonism of apomorphine and d-amphetamine effects by THIP (Fig. 3.9)

(f) AOAA produced EEG synchronization in the HS, OT and RF without significant effect on the EMG activity (Fig. 3.10). Administration of apomorphine in AOAA treated chicks produced synchronization of the waves in the HS, OT and markedly reduced EMG activity thus antagonizing the effects of apomorphine in all these areas.

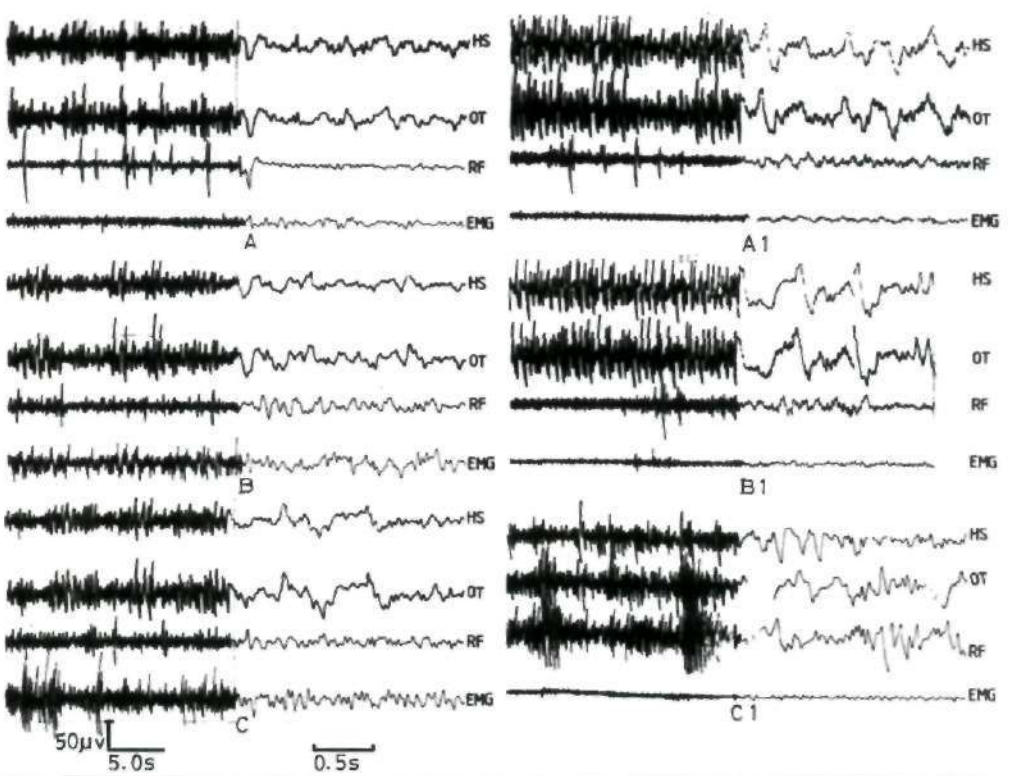


Fig. 3.8 Effect of GABA (100 mg/kg) interaction with APOM (0.125 mg/kg) and d-AMPHET (5 mg/kg) on EEG activity in young chicks. Pretreatment time was 15 min.
A/A_1 were saline controls
B/C^1 were the effects of GABA + APOM at 15 min/30 min.
B_1/C_1 were the effects of GABA + AMPHET at ^{1}30 min/60 min. post injection respectively.

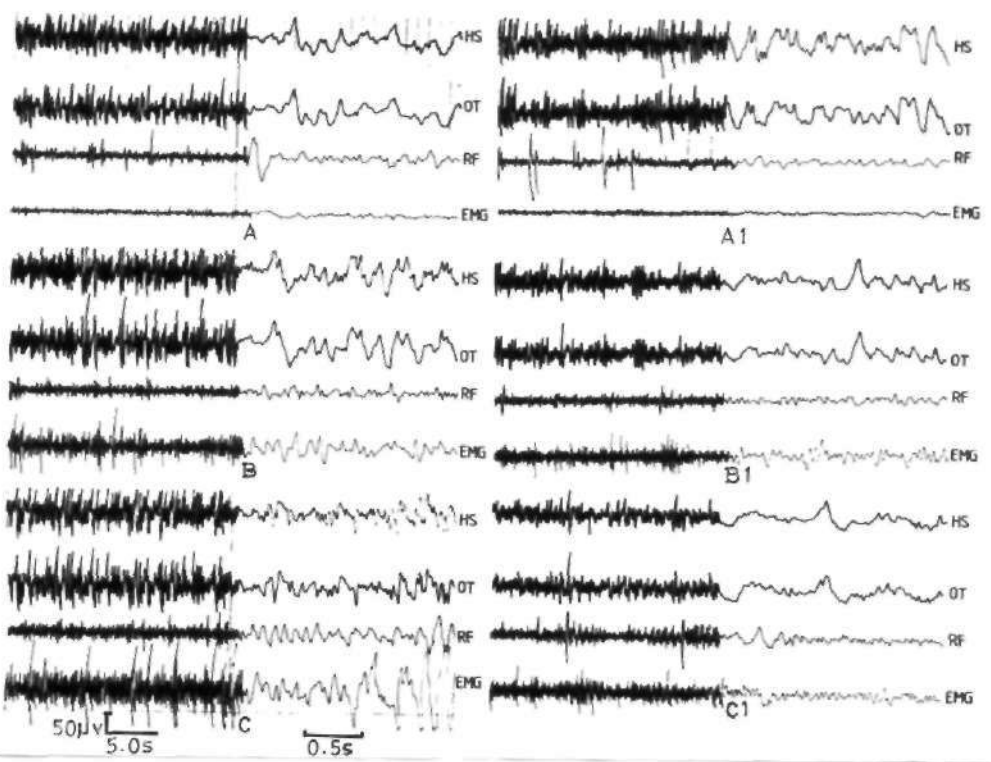


Fig. 3.9 Effect of THIP (0.20 mg/kg) interaction with APOM and d-AMPHET on EEG activity in young chicks. Pretreatment time was 15 min.
A/A_1 were saline controls
B/C^1 were the effects of THIP + APOM at 15 min/30 min.
B_1/C_1 were the effects of THIP + d-AMPHET at ^{1}30/60 min. post injection respectively.

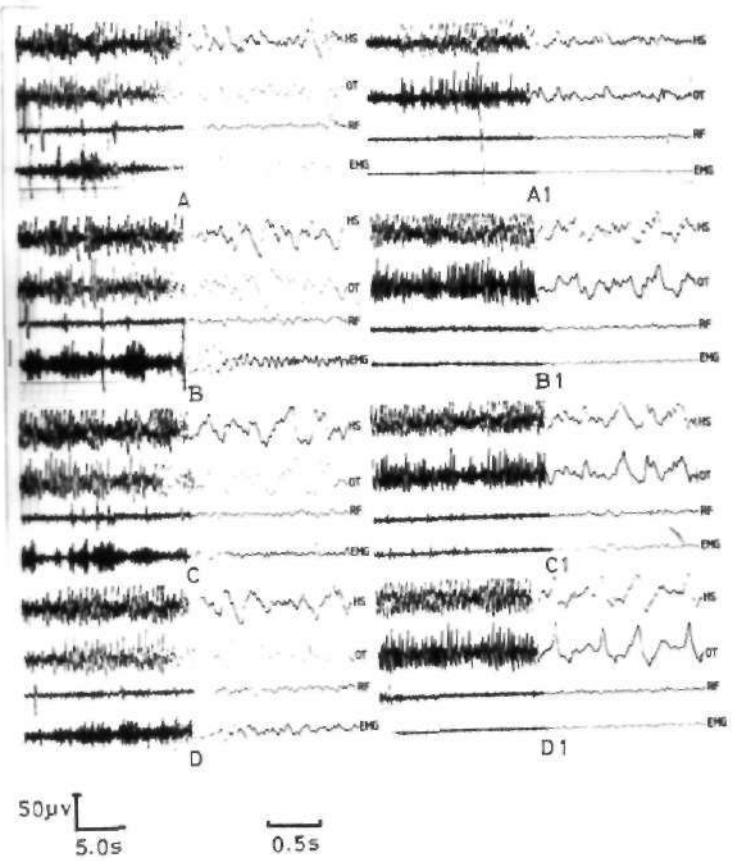


Fig. 3.10 Effects of GHB (50 mg/kg) and AOAA (2.5 mg/kg) on the EEG activity in young chicks.

A/A_1 Were saline controls

B/B_1 were the effects of GHB/AOAA at 15 mins.

C/C_1 were the effects of GHB/AOAA at 30 mins.

D/D_1 were the effects of GHB/ AOAA at 60 mins. post injection respectively.

On d-amphetamine, AOAA synchronized the waves in the HS, OT and also antagonized the EMG activation produced by d-amphetamine (Fig. 3.11).

(g) GHB produced synchronization of the waves in the HS, OT and RF with an accompanying increase in EMG activity (Fig. 3.10). Pretreatment with GHB 1 hour prior to administration of apomorphine produced slight synchronization of the OT and RF waves and increase in EMG activity after 15 mins. At 30 mins, there was synchronization of the waves in the HS, OT and RF and the EMG activation persisted. GHB also antagonized the EEG desynchronization produced by apomorphine and d-amphetamine resulting in low frequency, high amplitude waves but the EMG was activated (Fig. 3.12).

(h) Bicuculine produced desynchronization of the HS, OT and RF with accompanying, increase in EMG activity (Fig. 3.13). On apomorphine and d-amphetamine, bicuculine potentiated the EEG desynchronization produced by both drugs, in all the areas studied (Fig. 3.14).

3.4 Effect of some catecholaminergic agents on influence of GABAergic drugs on apomorphine and d-amphetamine-induced stereotyped behaviour.

(a) Reserpine (5 mg/kg) produced sedation in chicks.

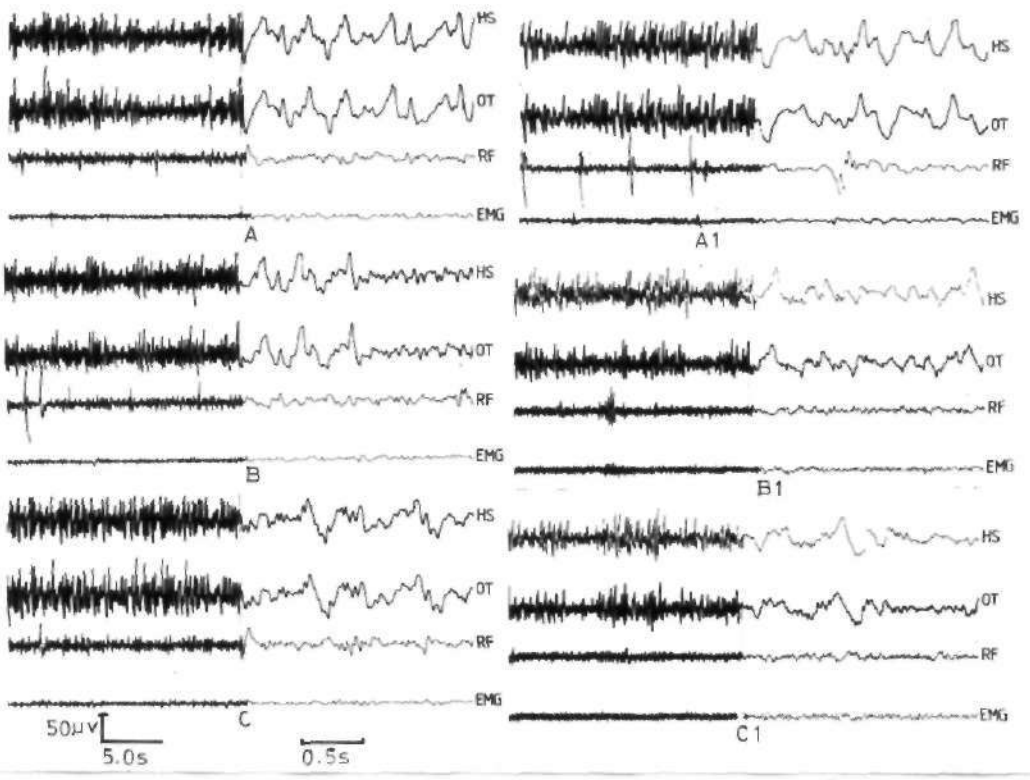


Fig. 3.11 Effect of AOAA (2.5 mg/kg) interaction with APOM and d-AMPHET on EEG activity in young chicks. Pretreatment time was 60 min.

A/A_1 were saline controls

B/C were the effects of AOAA + APOM at 15 min/30 min.

B_1/C_1 were the effects of AOAA + AMPHET at 30 min/60 min. post injection respectively.

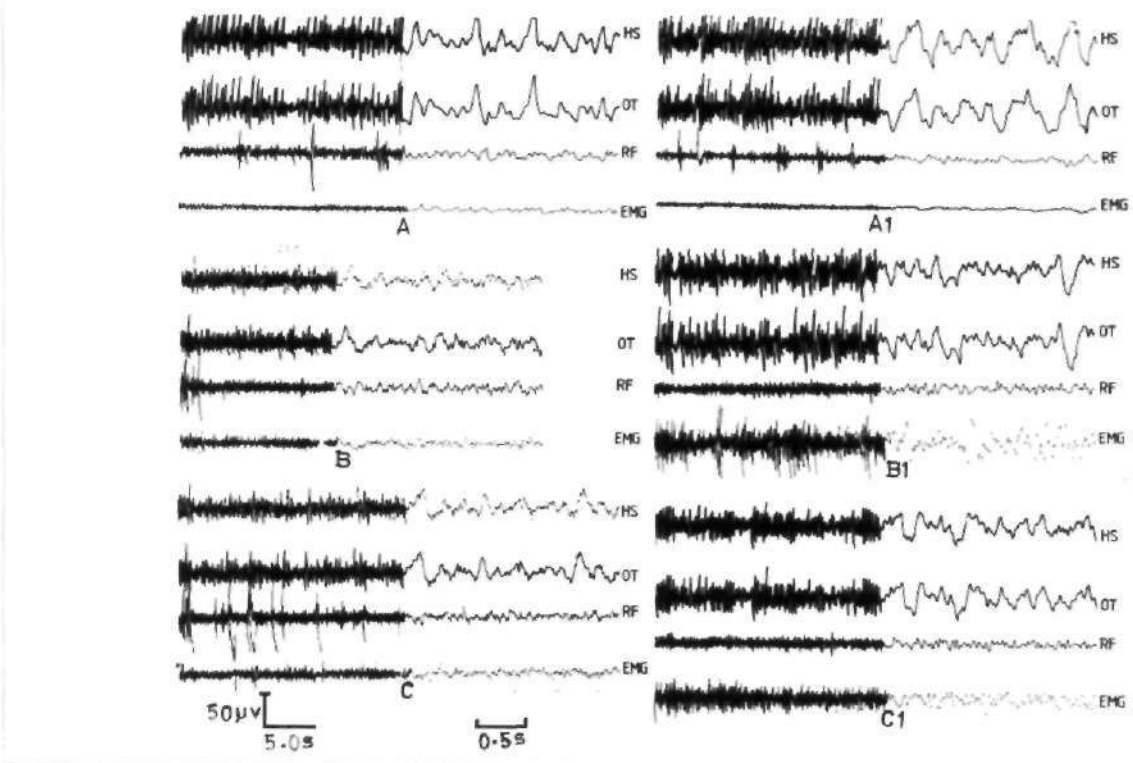


Fig. 3.12 Effect of GHB (50 mg/kg) interaction with APOM and d-AMPHET on EEG activity in young chicks. Pretreatment time was 60 mins.
A/A_1 were saline controls
B/C^1 were the effects of GHB + APOM at 15/30 mins.
B_1/C_1 were the effects of GHB + AMPHET at ^{1}30/60 mins. post injection respectively.

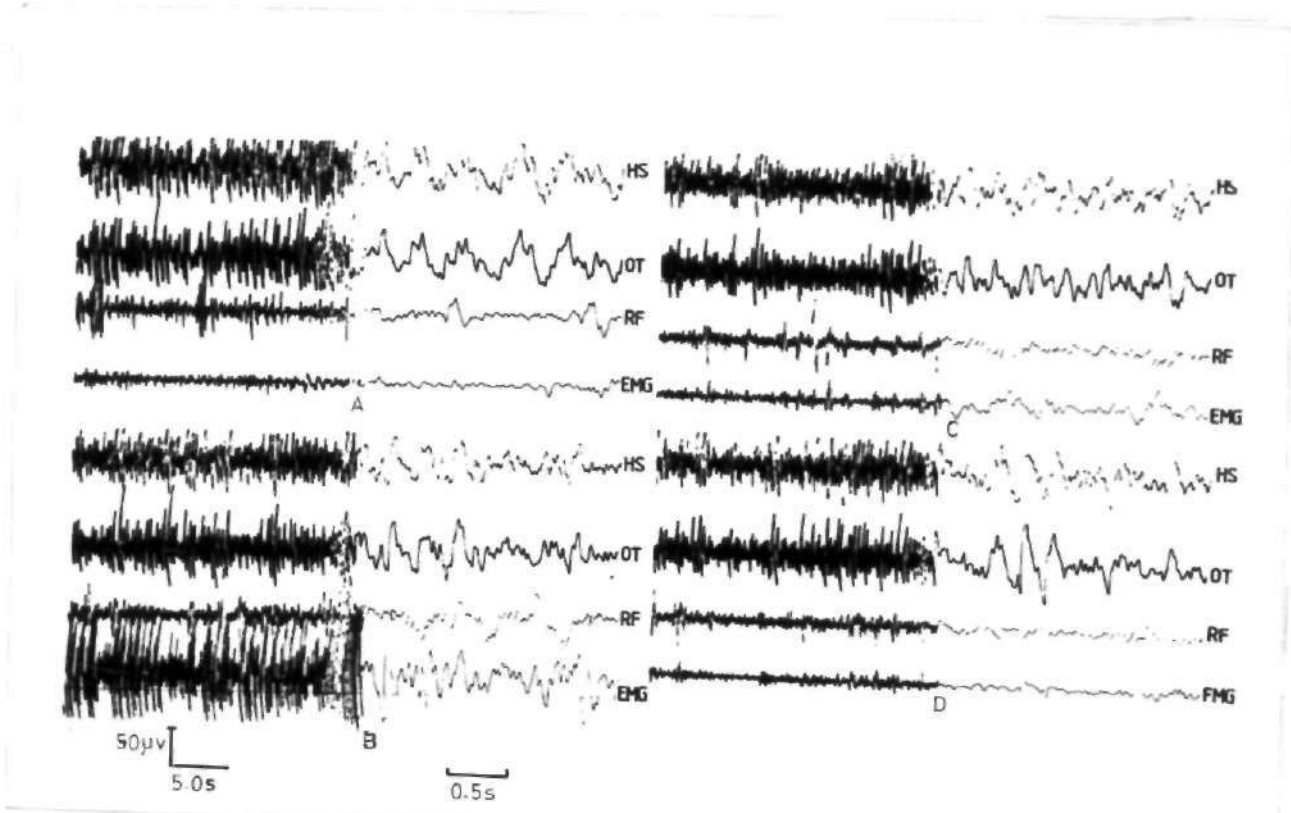


Fig. 3.13 Effect of BIC (5 mg/kg) on the EEG activity in young chicks.
A was the control
B was the effect 15 min post injection
C was the effect 30 min post injection
D was the effect 60 min post injection respectively.

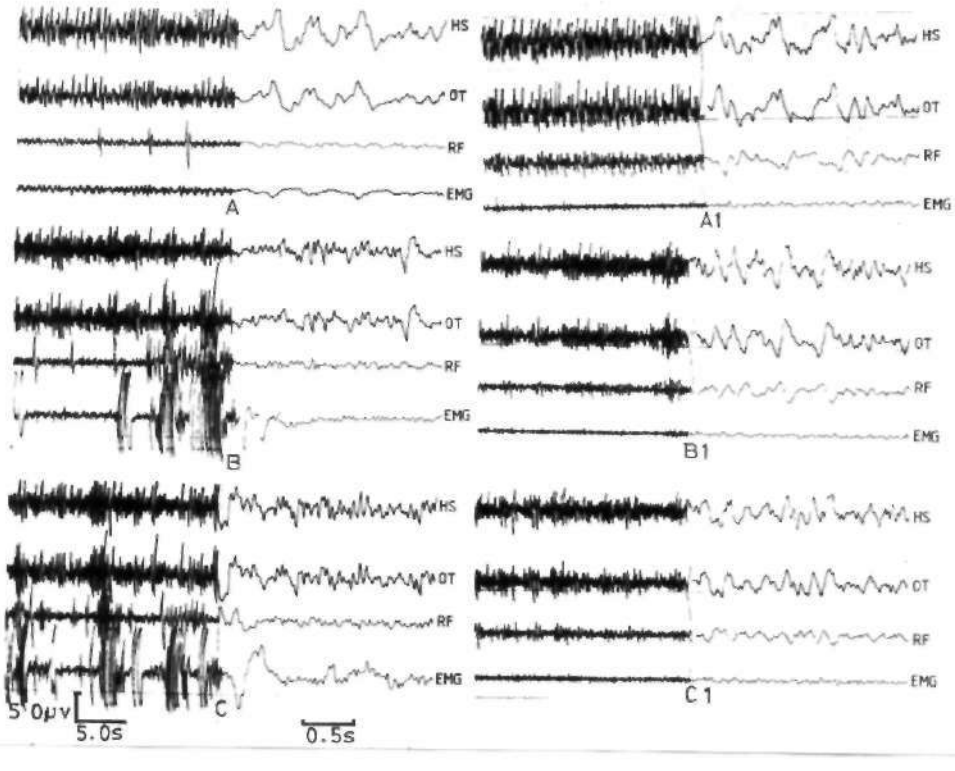


Fig. 3.14 Effect of BIC (5 mg/kg) interaction with APOM and d-AMPHET on EEG activity in young chicks. Pretreatment time was 15 min.

A/A_1 were the controls

B/C were the effects of BIC + APOM at 15min/30 min.

B_1/C_1 were the effects of BIC + AMPHET at 30 min/60 min. post injection respectively.

When administered 21 hours previously, it potentiated apomorphine effect and decreased onset of effect, while stereotyped behaviour induced by d-amphetamine was antagonized. Reserpine was observed to potentiate the effect of AOAA (2.5 mg/kg) on d-amphetamine-induced behaviour and antagonized the effect of AOAA (2.5 mg) and THIP (0.5 mg) on apomorphine-induced stereotyped behaviour (Fig. 3.15)

(b) Pimozide (1 mg/kg)

This dose of pimozide also produced sedation in chicks and when chicks were pretreated with the drug 1 hour previously, it antagonized both d-amphetamine and apomorphine-induced stereotyped behaviour.

Pimozide potentiated the inhibitory effect of GHB (50 mg/kg), AOAA (2.5 mg/kg), and THIP (0.2 mg/kg) on apomorphine (Fig. 3.16).

(c) FLA-63 (5 mg/kg) slightly potentiated pecking activities in the chicks. When administered 4 hours previously, it antagonized the effect of apomorphine while potentiating the effect of d-amphetamine.

FLA-63 potentiated the inhibitory effect of THIP (0.5 mg/kg) and AOAA (2.5 mg/kg) on apomorphine while it antagonized the inhibitory effect of AOAA on d-amphetamine (Fig. 3.17).

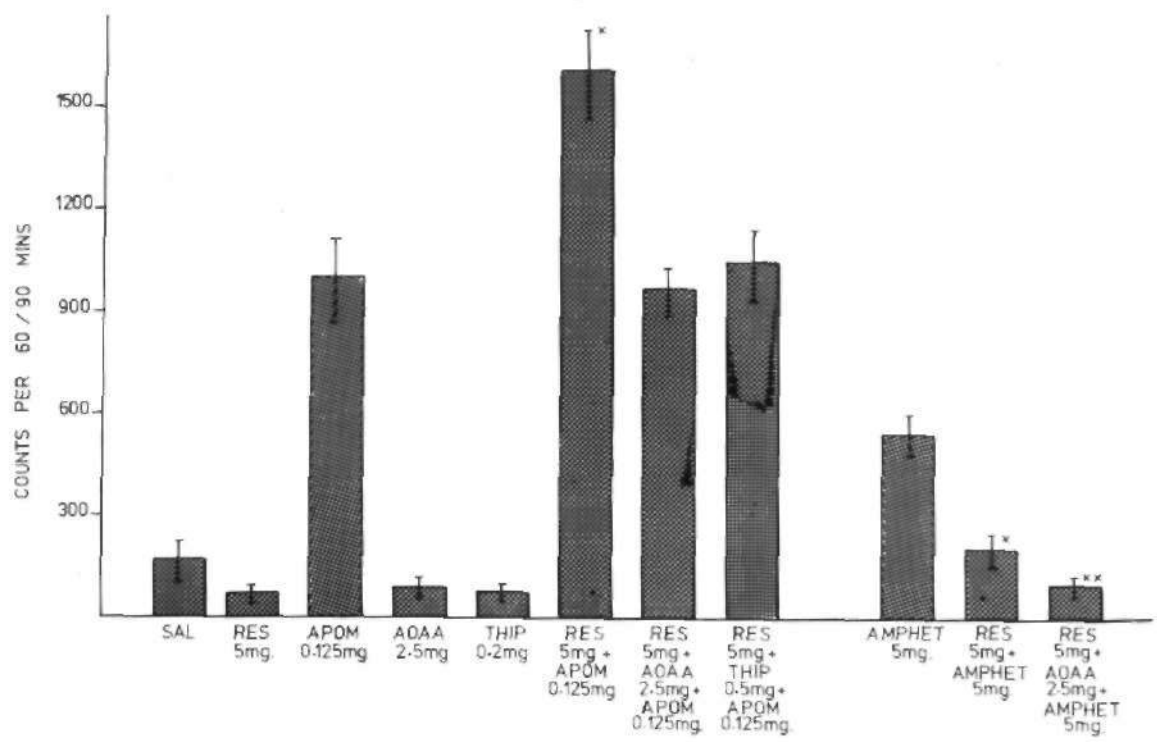


Fig. 3.15 Effect of Reserpine and its interaction with AOAA and THIP on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Chicks were pretreated with Reserpine 21 hours before administration of GABAergic drugs prior to apomorphine and d-amphetamine. Each histogram is the mean of total activity recorded. * and ** are significantly different from corresponding drug controls and represents $P < 0.001$ and $P < 0.05$, student's t - test. Vertical bars represent standard deviation (n = 6 pairs per histogram).

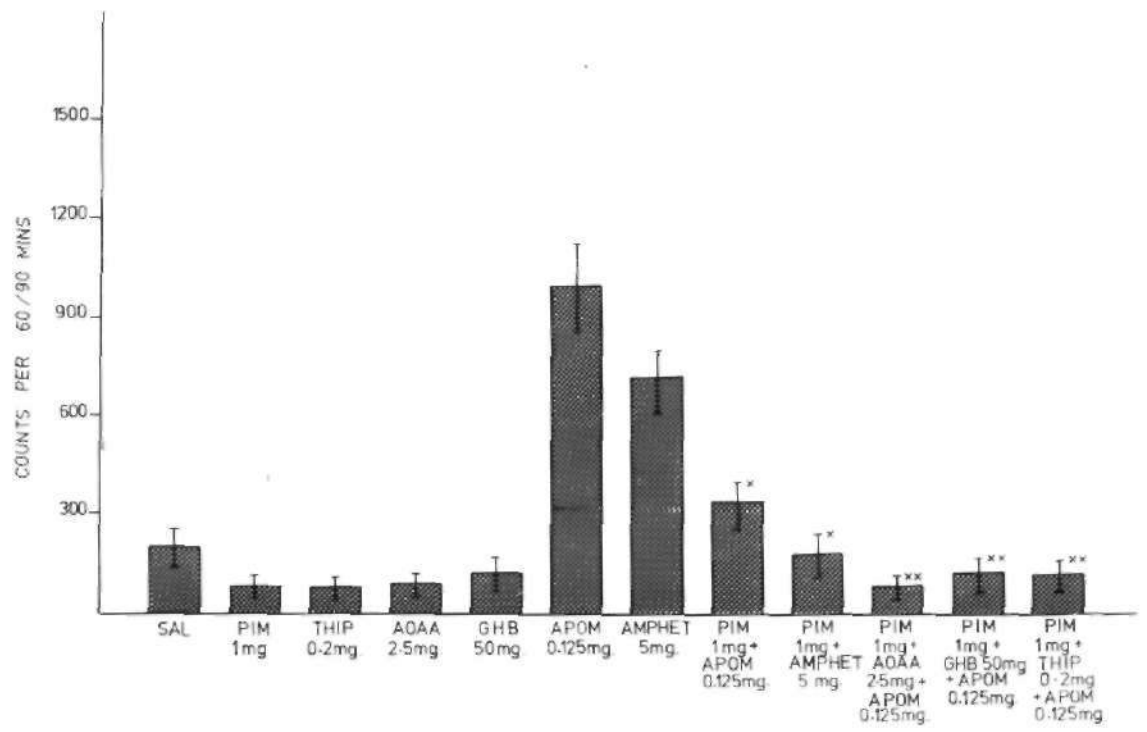


Fig. 3.16 Effect of Pimozide (PIM) and its interaction with AOAA, THIP and GHB on apomorphine- and d-amphetamine-induced stereotyped behaviour in young chicks. Chicks were pretreated with PIM 1 hour before administration of the GABAergic drugs prior to administration of apomorphine. Each histogram is the mean of total activity recorded. * and ** are significantly different from corresponding drug controls and represent $P < 0.001$ and $P < 0.05$, student's t - test. Vertical bars indicate standard deviation. (n = 6 pairs per histogram).

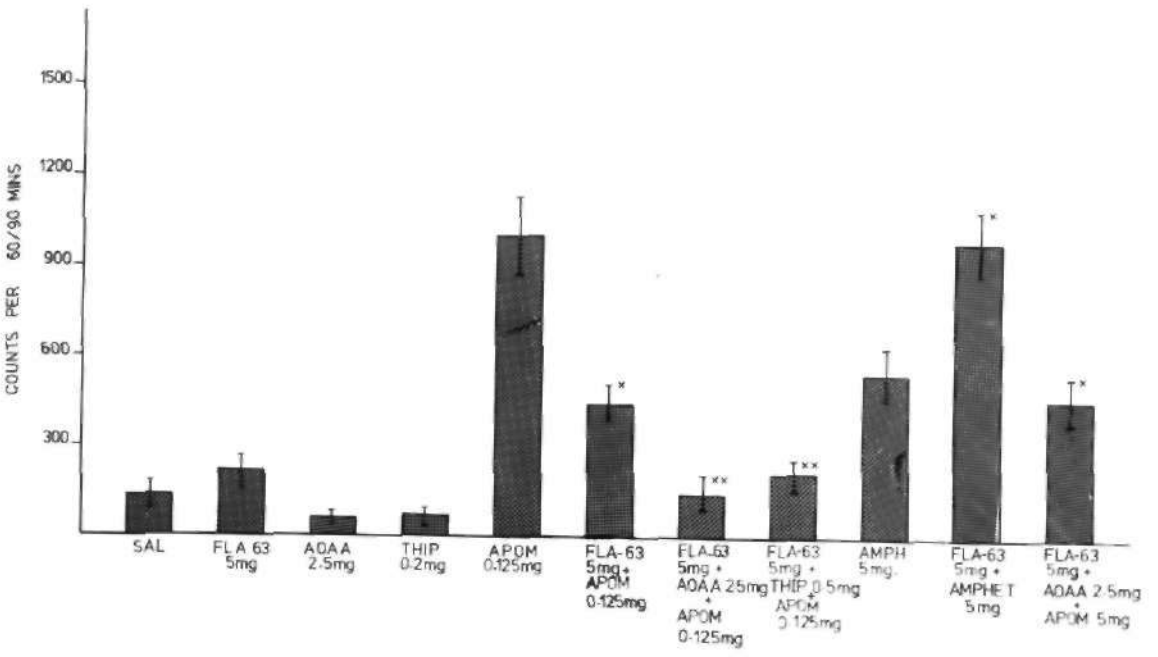


Fig. 3.17 Effect of FLA-63 and its interaction with AOAA and THIP on apomorphine and d-amphetamine-induced stereotyped behaviour in young chicks. Pretreatment time for FLA-63 was 4 hours while it was 15 mins for THIP and 1 hour for AOAA. Each histogram is the mean of total activity recorded. Vertical bars represent standard deviation. * and ** are significantly different from corresponding drug controls and represent $P < 0.001$ and $P < 0.05$, student's t - test (n = 6 pairs per histogram).

3.5 Influence of GABAergic agents on the behavioural effects of β'β'-iminodipropionitrile (IDPN)

With repeated administration of IDPN (300 mg/kg base) to rats, the ECC-syndrome appeared on the 7th day. It was characterized by circling and choreiform head and neck movements.

Circling behaviour was both clockwise and anti-clockwise. In some cases, the rats performed backward movements while the choreiform head and neck movements activity was being pursued.

During IDPN administration, the rats lost weight especially after the appearance of the ECC-syndrome probably due to increase in activity. The rats were however allowed one week to regain their weights and for the syndrome to be well established before being used for drug studies.

(a) D-amphetamine (2 mg/kg) potentiated both the circling and the choreiform head and neck movements in the rats.

(b) GHB (50-100 mg), AOAA (40 mg/kg), THIP (2-10 mg/kg) when administered alone inhibited the ECC-syndrome and also antagonized d-amphetamine-induced potentiation of the ECC-syndrome especially the circling behaviour (Fig. 3.18 - 3.20). These effects were more pronounced in the first 30 mins of the experiment.

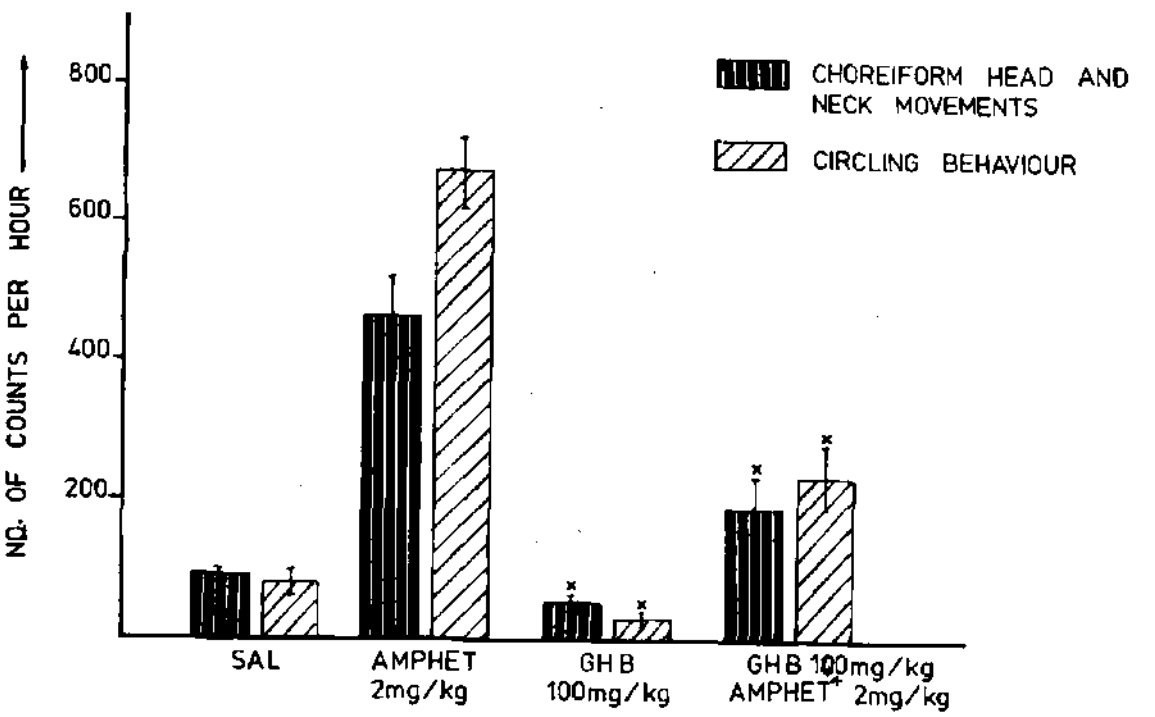


Fig. 3.18 Effect of Gamma-hydroxybutyric acid GHB) and its interaction with d-amphetamine (AMPHET) on IDPN-induced choreiform head and neck movements and circling behaviour in rats. Rats were pretreated with GHB 30 mins prior to administration of d-amphetamine. Vertical bars represent standard deviation.
* is significantly different from saline and the drug controls and represents $P < 0.001$, student's t - test.
(n = 6 rats per histogram)

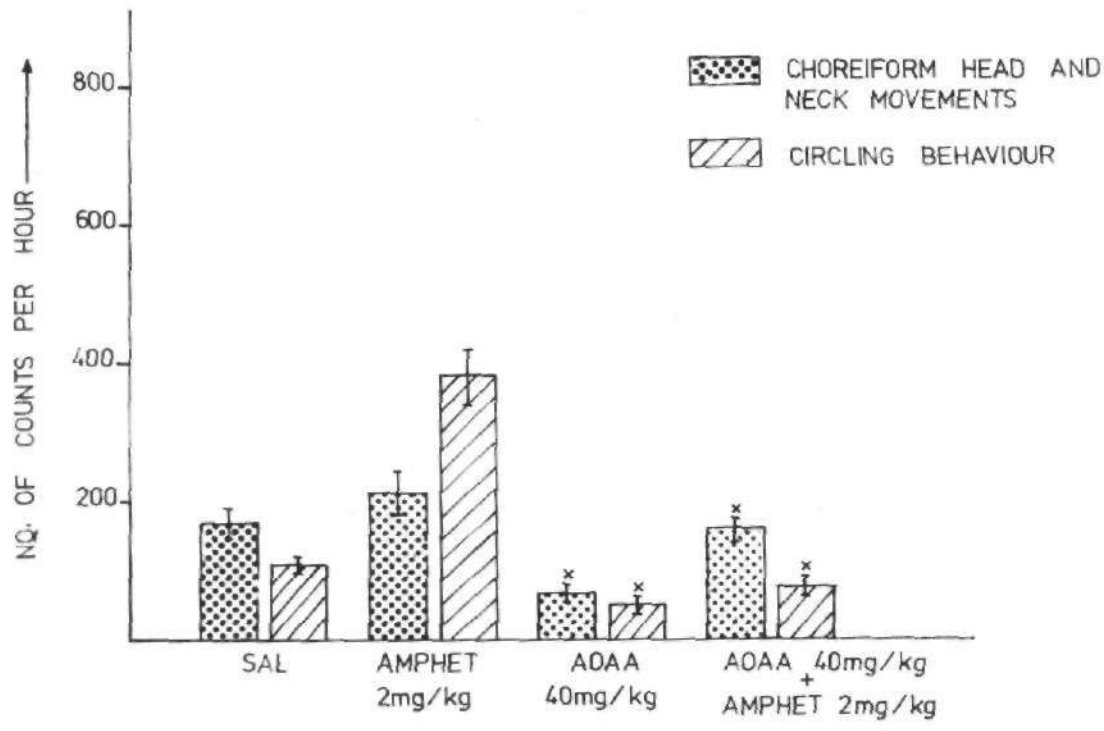


Fig. 3.19 *Effect of* aminooxyacetic acid (AOAA) and its interaction with d-amphetamine (AMPHET) on IDPN-induced choreiform head and neck movements and circling behaviour in rats. Rats were pretreated with AOAA 30 mins prior to administration of d-amphetamine. Vertical bars represent standard deviation. * is significantly different from saline and drug controls and represents $P < 0.001$, student's t - test. (n = 6 rats per histogram).

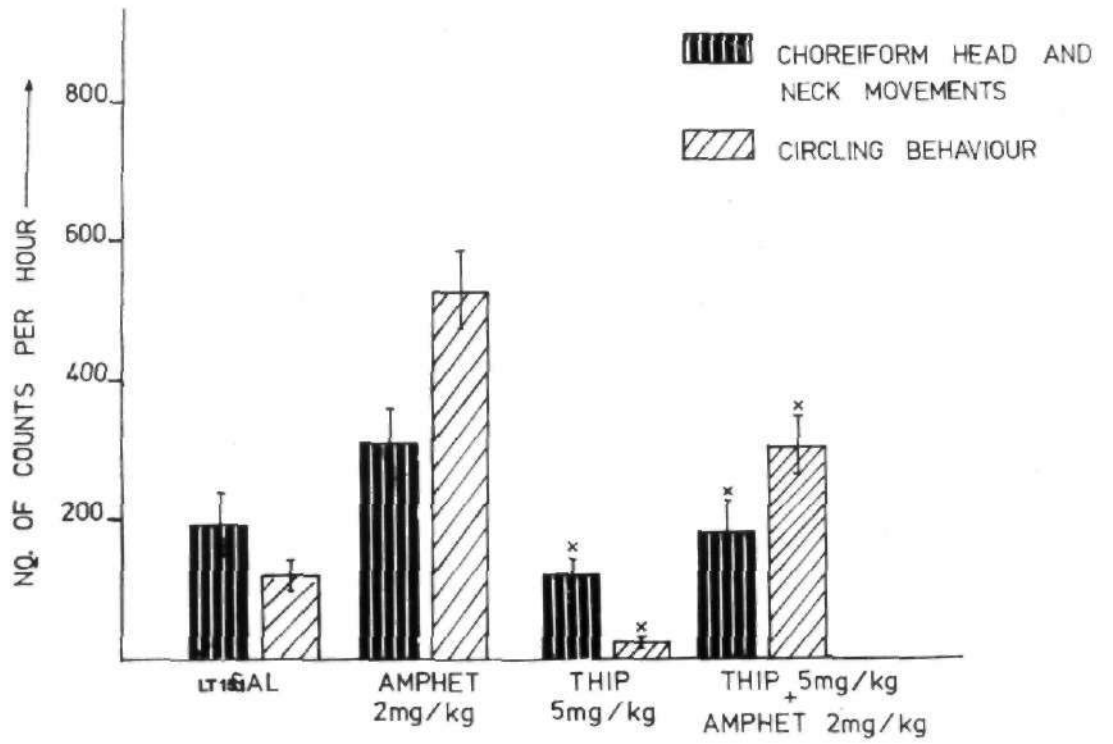


Fig. 3.20 Effect of (4,5,6,7-tetrahydroisoxazolo-5,4-c-pyridin-3-ol (THIP) and its interaction with d-amphetamine (AMPHET) on IDPN-induced choreiform head and neck movements and circling behaviour in rats. The rats were pretreated with THIP 30 mins prior to administration of d-amphetamine. Vertical bars represent standard deviation (n = 6 rats per histogram). * is significantly different from saline and the drug controls and represents $P < 0.001$, student's t - test.

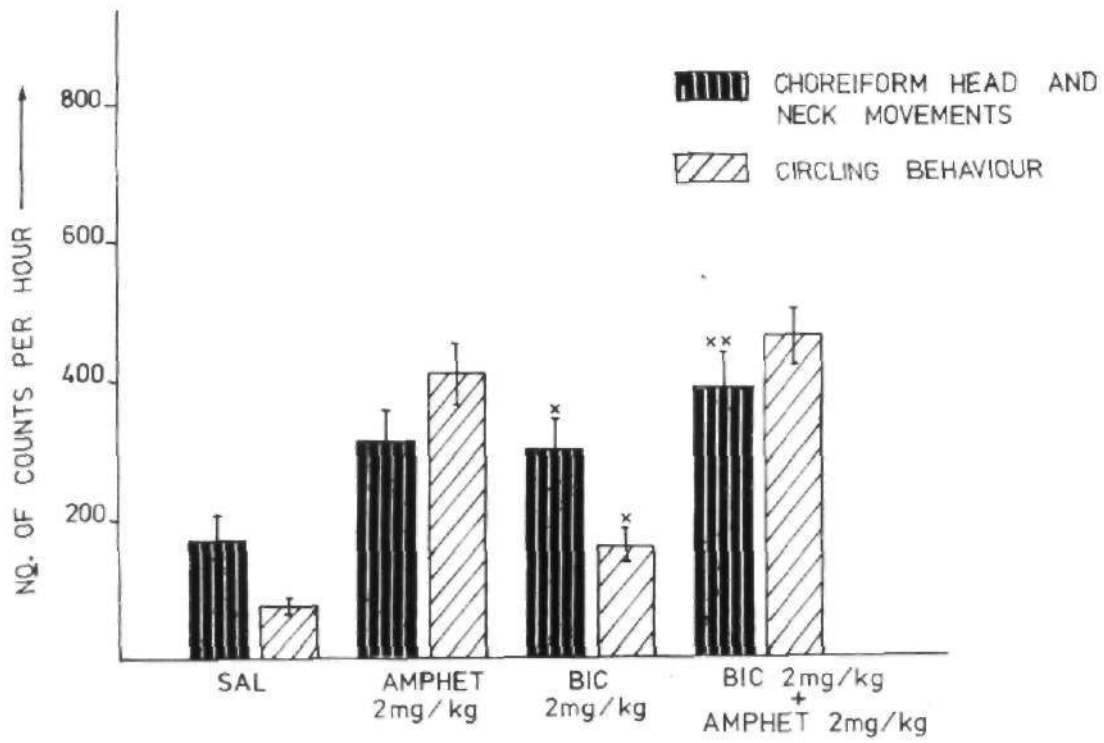


Fig. 3.21 Effect of bicuculine (BIC) and its interaction with d-amphetamine (AMPHET) on IDPN-induced choreiform head and neck movements and circling behaviour in rats. Rats were pretreated with BIC 30 mins prior to administration of d-amphetamine. Vertical bars represent standard deviation (n = 6 per histogram). * and ** are significantly different from saline and the drug controls and represent $P \leq 0.005$ and $P < 0.05$, student's t - test.

(c) Bicuculine (2-10 mg/kg) potentiated both the choreiform head and neck movements and circling in the rats. Bicuculine also potentiated (though non-significantly) the effects of d-amphetamine on the syndrome (Fig. 3.21).

CHAPTER 4

DISCUSSION AND CONCLUSIONS

The observed behavioural effects induced by apomorphine and d-amphetamine in the chicks are similar to those reported by previous workers (Osuide and Adejoh, 1973; Schrold and Squires, 1971). Both drugs produced stereotyped behaviour characterized by the chicks pecking, at their own body and feet, at those of the partners, at non-food objects including the walls and floor of the cage and also by agressive and fighting episodes. Dopaminergic system has been associated with stereotyped behaviour (Randrup and Jonas, 1967), and most of the drugs that produce this stereotyped behaviour affect the striatum and related areas of the brain that have been observed to contain high concentration of DA in both mammalian and avian species (Hornykiewicz, 1966).

Apomorphine is believed to produce its behavioural effects in various species by stimulating DA receptors directly (Ernst, 1967; Andén et al, 1967). On the other hand, d-amphetamine is considered to produce its effect indirectly by releasing catecholamine and inhibiting monoamine oxidase enzyme (Carlsson et al, 1965; Glowinski, 1966) although some workers have also reported its direct stimulant effect on DA receptors (Van Rossum et al, 1964). The reason for the observed weaker effect of d-amphetamine in inducing stereotyped behaviour as compared to apomorphine is not very clear from this study and this requires further elucidation. However, d-amphetamine also releases 5-HT and noradrenaline and these neurotransmitters have been reported to have inhibitory effect

on drug-induced stereotyped behaviour (Weiner et al, 1973 and Mogilnicka and Braestrup, 1976). Thus the influence of d-amphetamine on these neurotransmitters systems may be contributing to its lower potency in inducing stereotyped behaviour in young chicks as compared to apomorphine.

The postural effects observed with d-amphetamine are similar to those reported by Schrold and Squires, (1971). According to these workers, d-amphetamine may be producing these effects via a serotonergic mechanism. GABA does not cross blood-brain barrier and large doses of GABA have been observed not to produce significant increases in brain GABA levels (Purpura et al, 1958; Roberts, 1958). However intraperitoneal injection of GABA in large doses has been shown to cross the blood-brain barrier in young chicks (Scholes, 1965; Kramer et al. 1967). This is due to immature blood-brain barrier in young chicks (Waelsch, 1965; Key and Marley, 1962). Thus GABA so administered increases GABA levels in the brain of these chicks. GABA has been shown by many workers as the major inhibitory transmitter in the central nervous system (Curtis and Watkins, 1960; Fahn and Coté, 1968; Okada et al, 1971). It produces its inhibitory action both pre- and post-synaptically. Presynaptically, GABA produces depolarization of terminals of afferent fibres and depresses release of excitatory transmitters from these terminals (Eccles, 1964; Walberg, 1966) while post-synaptically, GABA inhibits firing of cortical neurons thus reducing excitability and depressing excitatory post-synaptic potentials (EPSPs)(Curtis and Watkins, 1960; Krnjević, 1978).

The observed depressant or sedative effects after administration of GABA in chicks may be due to these actions of GABA. THIP is a potent and specific GABA-receptor agonist (Scheel-Kruger et al, 1978). It thus produces its behavioural effects by stimulating GABA receptors directly. The observed behavioural depressant effect of THIP in the chick is probably due to this stimulation of GABA receptors. AOAA increases GABA levels in brain by exerting a powerful and prolonged inhibition of GABA-T activity (Wallach, 1964; Baxter and Roberts 1961) thus preventing GABA metabolism and promoting accumulation of GABA. This effect of AOAA is more pronounced at lower doses and may account for the behavioural depressant effect observed in the chicks at these doses. The convulsant effect observed at higher doses is probably because at these doses, AOAA inhibits GAD activity (Wallach, 1961; Osuide 1972) thus inhibiting GABA formation and rendering the chicks susceptible to epileptogenic stimuli.

Intraperitoneal injection of GHB has been shown to increase brain GABA levels in chicks (Sisken et al, 1960) and also to inhibit unit activity in substantia nigra (Pericic et al, 1978) The observed sedative effect of this drug at low doses is also probably due to increase in GABA levels. Similar observations have been made in man and other mammalian species (Laborit et al, 1960; Jouany et al 1960 a and b). The reported excitatory

effect of GHB at high doses may probably be due to a selective increase in DA concentration (Gessa et al, 1966). Bicuculine is a fairly potent, specific and competitive antagonist of GABA (Curtis et al, 1971; Johnston, 1976). It has also been shown to have a direct action on nerve axon (Freeman, 1974) and muscle or muscle-membrane leading to increase in excitability of these structures. The observed excitatory effect of bicuculine characterized mainly by pecking at non-food objects might be due to this blockade of GABA receptors. There have been differences of opinion as to the value of bicuculine as a GABA antagonist at cortical synapses: while it has been observed to produce reversible antagonism of depressant action of GABA by some workers (Johnston, 1976; McLennan, 1970b and 1973), other workers have found it ineffective (Straughan et al, 1971; Swagel et al, 1974). This is probably partly due to the fact that bicuculine weakly inhibits uptake of GABA in brain (Olsen, 1976). In addition, when given intravenously, its action is not restricted to one specific area of the brain. These effects coupled with anatomical complexity of the cerebral cortex would probably account for the differences so observed.

GABA and its synthesizing enzyme, GAD have been shown to be particularly abundant in globus pallidus, substantia nigra and striatum (Fahn, 1976)

which are areas with high DA function. Thus, DA coexists in the substantia nigra with other neurotransmitters of which GABA is one and important interactions have been shown to occur within this area. Furthermore, there are GABA containing terminals in substantia nigra belonging to neurons originating in the striatum (Feltz, 1971; Fonnum et al, 1971). The descending striato-nigral pathway has been shown to be inhibitory and it is GABA-mediated and it is this pathway that has been shown to be involved in the neuronal feedback loop regulating the activity of DA neurons.

From the above, the observed antagonism of apomorphine and d-amphetamine-induced stereotyped behaviour by GABA, THIP, AOAA and GHB might be due to activation of the descending inhibitory GABA-ergic pathway thus clamping down on the excitatory action of DA and DA agonists. Bicuculine (5 mg/kg) was observed to significantly potentiate the stereotypies induced by both apomorphine and d-amphetamine and also to antagonize the effect of AOAA, GABA and THIP on apomorphine-induced stereotyped behaviours. This enhancement of activity of DA agonists could be related to blockade of the inhibitory control of DA by both endogenous and administered GABA.

The EEG desynchronization observed with apomorphine and d-amphetamine is consistent with the observed behavioural excitatory effects of these drugs. The antagonism of these effects by GABA, GHB, AOAA and THIP and potentiation by bicuculine

supports the observations made in the behavioural studies. These observations suggest that in the chick, agents that activate GABAergic mechanisms have a predominant inhibitory role on behavioural excitation produced by dopamine agonists. This probably reflects the mutual antagonism which exists between GABA and dopamine in the central nervous system. The mechanism of EMG activation by some GABA-mimetic drugs after DA agonist is not evident from this study. These effects may probably due to a direct effect on the muscle resulting in enhancement of EMG activation produced by the DA agonist.

Reserpine has been shown to deplete catecholamines and serotonin in brain (Bertler et al, 1956) and their receptors have also been observed to become more sensitive to stimulation after the depletion be it on long- or short-term basis (Ungerstedt 1971b; Costentin et al, 1975). The observed potentiation of apomorphine stereotypy could then be attributed to increased sensitivity of the DA receptors to apomorphine. In this study, Reserpine has been observed to antagonise d-amphetamine-induced stereotyped behaviour. This is in contrast to the observation made in rats by other workers. In these studies, reserpine pretreatment had no influence on d-amphetamine-induced effects and it was suggested that both drugs may be acting on different monoamine pools (Rech, 1964). The observed antagonism of d-amphetamine effects by reserpine in the present study suggests that in young chicks, these drugs may be acting on the same dopamine pool. Neurochemical studies are required to elucidate the exact mechanisms involved in this interaction. The increase in GABA level produced by AOAA was probably responsible for the potentiation of the inhibitory effect of AOAA on d-amphetamine-induced stereotypy whereas the increase in the sensitivity of the receptors

to DA was probably responsible for the antagonism of the inhibitory effects of THIP (0.5mg/kg,) and AOAA (2.5mg/kg) on apomorphine-induced stereotyped behaviour. The fact that higher doses of THIP were required to produce significant effect further indicates that the DA receptors were more sensitive to apomorphine after pretreatment with reserpine.

Pimozide is a specific DA receptor blocker (Anden et al, 1970; Janssen et al, 1965) whereas apomorphine is known to be a direct acting DA agonist. With blockade of DA receptor sites by pimozide, apomorphine and d-amphetamine will be of no effect hence the observed antagonism of apomorphine and d-amphetamine effect by pimozide. In addition, pimozide and the butyrophenone-like neuroleptics have been observed to mimic the action of GABA and GABA receptors (Mariyama and Kawasaki, 1976) though this is said to be secondary to the DA receptor blocking action. This effect coupled with the inhibitory effect of the GABAergic agents, GHB, AOAA and THIP could account for the increase in antistereotypic effect observed with these GABAergic agents on apomorphine after additional treatment with pimozide.

FLA-63 is a DA β-hydroxylase enzyme inhibitor thereby increasing the level of DA in brain (Corrodi et al, 1970). The mechanism of antagonism of apomorphine effect produced by FLA-63 is not clear from this study and further

work needs to be done to elucidate it. The potentiation of d-amphetamine-induced stereotyped behaviour was probably due to the increased amount of DA available for release by d-amphetamine. The potentiation of the inhibitory effect of AOAA and THIP by FLA-63 on apomorphine is probably a summation of the inhibitory effect of FLA-63 alone on apomorphine and the inhibitory effect of the GABA-mimetics on apomorphine.

The increase in DA levels may be responsible for the failure of AOAA to antagonize d-amphetamine-induced stereotyped behaviour. It follows then that increase in DA level is able to antagonize GABA effects.

Other neurotransmitter systems that have been observed to play a role in stereotyped behaviour may also be involved in GABA feedback control of DA activity. For example, serotonergic system has been reported by some workers to have an inhibitory effect on drug-induced stereotyped behaviour (Weiner et al, 1973; Chen and Long, 1974; Saxena et al, 1977). Increase in GABA level produced by GABA and GABA-T inhibitor have been shown to elevate brain serotonin level (Buniatian and Yessian, 1968; Yessian et al, 1969). This increased level of serotonin could contribute to the observed inhibitory effect of GABAergic agents.

From the results obtained in this study, GABA agonist and GABA-mimetic drugs were observed

not to induce stereotyped behaviour per se in the chicks and that GABAergic mechanism seems to have an inhibitory influence on dopamine which is believed to be involved in inducing stereotyped behaviour. This assumption thus conforms with the earlier concept of existence of GABAergic mechanism possessing an inhibitory influence on DA pathways. Electrophysiological studies have shown that iontophoressed GABA depresses the activity of cells in the substantia nigra in both zona compacta (Aghajanian and Bunney, 1978) and reticulata (Crossman et al, 1973). Pharmacological studies also support the idea of inhibitory striatonigral feedback loop controlling the activity of DA (Andén and Stock, 1973). In addition, immunocytochemical studies have revealed localization of GAD in both zona compacta and zona reticulata (Ribak et al, 1976) thus suggesting the evidence of a direct synaptic contact between GABAergic terminals and the DA cell bodies in the zona compacta of substantia nigra.

D-amphetamine and apomorphine-induced stereotyped behaviour is widely accepted as a model of psychosis and it is used for screening potential anti-psychotic agents. Currently, it has been proposed that the defect in schizophrenia may not lie in the overactivity of DA alone but rather in its activity relative to other neurotransmitter systems (Roberts, 1972). The observed

inhibition of d-amphetamine and apomorphine-induced behavioural and EEG effects by GABAergic agents used in this study suggests that these drugs may have possible beneficial effects in psychosis. Baxter et al (1978) suggested that d-amphetamine-induced EEG effects in rats could be a possible test for potential anti-psychotic agents. However, earlier clinical trials using GABA and GABA-mimetic drugs have not produced beneficial effects in schizophrenic patients (Taminga et al, 1978; Chase and Taminga, 1979). More recent data using rats and mice have questioned the inhibitory effect of GABA on DA (Scheel-Kruger et al, 1977; 1978; Cheramy et al, 1978; Christensen et al, 1978; Olianas et al, 1978). In these studies, while GABA agonist especially muscimol and THIP facilitate or mediate dopaminergic effects in some models, in others, they attenuate DA effects. However, lesion studies in crus cerebri which produces significant increase in DA release also produced a consequent decrease in GABA content of substantia nigra (Racagni et al, 1977). Furthermore, increases in GABA levels caused by GABA-T inhibitor in substantia nigra has also been shown by some workers to cause consequent decrease in striatal DA release. These data in agreement with the electrophysiological studies seem to suggest that GABA exerts an inhibitory influence on DA in the striatum. However, it must be admitted that a more complex situation might also

be operative considering the co-existence of many putative neurotransmitters in substantia nigra and the interaction that could occur. Also, on the evidence for an excitatory role of nigral GABAergic terminals, it has been suggested that neuronal pathways other than those involving DA may be involved as reserpine (Arnt et al, 1979) and haloperidol (Oberlander et al, 1977) have been shown not to antagonize this excitatory effect.

On the hyperkinetic syndrome elicited by repeated administration of IDPN, d-amphetamine was observed to potentiate both the choreiform head and neck movements and the circling as has been reported by other workers like Gabay et al, (1974) in rats and Sokomba and Osuide (1983) in chicks. These workers suggested that DA may play a role in IDPN-induced behavioural effects. DA has been implicated as the major catecholamine involved in d-amphetamine-induced behavioural effects. Thus the observed potentiation of the syndrome by d-amphetamine may be due to activation of DA mechanisms. This is further supported by the reported inhibition of the syndrome and d-amphetamine effect by pimozide (Gabay et al, 1974), THIP, GHB and AOAA antagonized the circling and choreiform head and neck movements and d-amphetamine-induced potentiation of the syndrome in these rats. Bicuculine, (a fairly

potent GABA receptor antagonist) potentiated both the circling and choreiform head and neck movements. This suggests that activation of GABAergic mechanisms attenuates the ECC-syndrome while the latter is exacerbated after blockade of GABAergic activity. The observations further suggest that GABA and DA may be exerting opposing effects on this syndrome. According to Langlai et al, (1975), DA levels are not significantly altered in syndromized rats, thus IDPN may not be acting directly on dopaminergic system to produce the ECC-syndrome. It is however possible that dopaminergic system may be affected indirectly via other neurotransmitter systems that normally modulate DA activity. A decrease in the level of a transmitter substance that normally modulates DA activity would lead to enhancement of the effects of the latter. Consistent with this, low brain levels of GABA have been associated with the ECC-syndrome (Sconzert et al, unpublished observation) and this may be contributing to the mechanisms underlying the syndrome. In addition, further studies have indicated the possible involvement of other neurotransmitter systems such as serotonergic and cholinergic systems in this syndrome (Langlais et al, 1975; Sokomba and Osuide, 1983) thus the overall picture of this hyperkinetic syndrome may be due to multiple transmitter involvement. Further studies are required to

elucidate the precise mechanism underlying the behavioural effects of IDPN.

In conclusion, the observations made in this study show that in young chicks, GABAmimetic drugs produced dose-dependent behavioural depression and that GABAergic mechanism seems to play an inhibitory influence on DA system involved in inducing stereotyped behaviour. Results obtained from EEG studies confirmed these behavioural observations. These observations are not in agreement with recent data in mice and rats which indicate that some GABA agonists (especially muscimol and THIP) facilitate or mediate dopaminergic effects (Christensen et al, 1978 and Scheel-Kruger et al, 1977, 1978). They however, supported the old concept of GABAergic mechanism possessing an inhibitory influence on DA pathways.

On the hyperkinetic syndrome elicited by repeatedadministration of IDPN in rats, the observations suggest a possible role for GABA in the behavioural effects of IDPN and further, that GABA and DA may be exerting opposing effects on the syndrome.

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