BIOCHEMICAL EFFECT OF SOME TRANQILIZERS ON CERTAIN LIVING CELLS

THESIS SUBMITTED

BY

INASS IBRAHIM EL-GAAFRAWY

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Biochemistry Department

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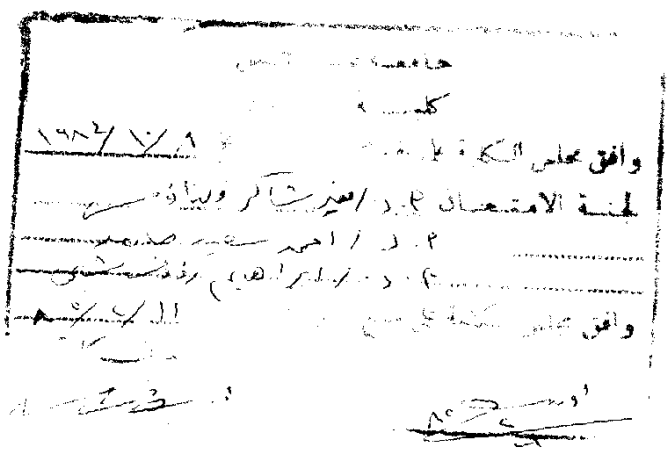
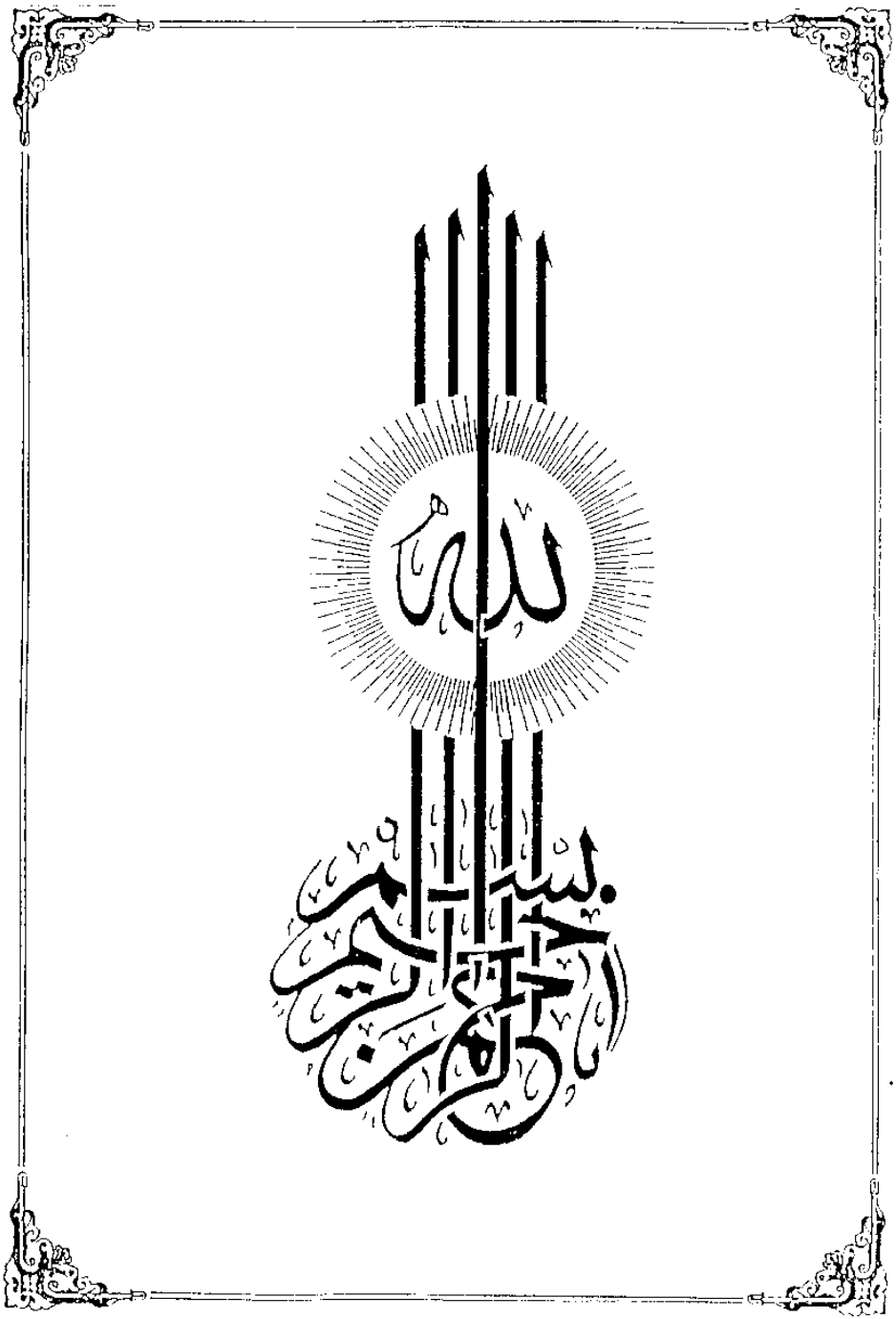
This thesis has not been submitted for a degree at this or any other university.

Inass Ibrahim El-Gaafrawy





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ABBREVIATIONS

A/G ratio	=	*Albumin per globulin ratio*
ACTH	=	*Corticotrophin hormone*
ATP	=	*Adenosine triphosphate*
B. subtilis	=	*Bacillus subtilis*
C	=	*Degree centigrade*
CNS	=	*Central nervous system*
DNA	=	*Deoxyribonucleic acid*
DOPAC	=	*Dihydroxy phenylacetic acid*
E. coli	=	*Escherichia coli*
g	=	*Gram*
Kg	=	*Kilogram*
L	=	*Liter*
M	=	*Molar*
mg	=	*Milligram*
MIC	=	*Minimum inhibitory concentration*
ml	=	*Milliliter*
mM	=	*Millimole*
N	=	*Normality*
NAD	=	*Nicotinamide adenine dinucleotides*
nm	=	*Nanomiter*
O.D.	=	*Optical density*
RNA	=	*Ribonucleic acid*
r.p.m.	=	*Round per minute*
s. typhosa	=	*Salmonella typhosa*
S. RNA	=	*Soluble ribonucleic acid*
St. aureus	=	*Staphylococcus aureus*

TCA	=	*Trichloroacetic acid*
U	=	*Unit*
ug	=	*Microgram*
ul	=	*Microliter*
v/v	=	*Volume per volume*
w/v	=	*Weight per volume.*
%	=	*Per cent*

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PREFACE

Stressing effects caused by modern civilization on individuals led to the widespread use of psychotropic drugs known as "Tranquilizers" which were misused by the elapse of time to the level that are now considered as narcotic drugs. Tranquilizers are classified into two groups: major tranquilizers or neuroleptics and minor tranquilizers or anxiolytic sedatives.

The present study is mainly devoted to examine some metabolic effects of the minor tranquilizer, meprobamate on some living cells. Meprobamate is now used on a wide scale for the treatment of anxiety. There is evidence that the drug exerts multiple effects on the central nervous system. It selectively depresses the thalamus and inhibits evoked seizure discharges in the limbic system, thus reducing emotional tension.

In the present thesis biochemical studies of meprobamate effects are carried out on some selected living cells to explore its possible mode of action on this cells. Some inhibitory effects on the growth of E. coli cells was observed. The mode of action of meprobamate on E. coli NRRL B-3704 was carried out to examine the metabolic changes induced by the drug on the biosynthesis of macromolecules and related metabolites. Meprobamate exerted significant inhibitory effect on the biosynthesis of RNA and DNA by the bacterial cells. Excpectedly, such an effect was consequently reflected on the biosynthesis of proteins and lipids.

The biochemical effects of acute and chronic administration of meprobamate in adult male rats (Rattus Norvegicus) were also examined. Meprobamate, especially chronic doses influenced the normal levels of DNA, proteins and lipid fractions.

Meprobamate significantly reduced the contents of serum total protein, total globulin, phospholipids and cholinesterase activity; liver total protein, total globulin, DNA, phospholipids, glucosamine and cholinesterase activity ; brain total protein, albumin, total globulin, DNA, glucosamine and cholinesterase activity. The drug also increases serum triglycerides, free fatty acids, glucosamine, uric acid ; liver triglycerides and free fatty acids. This alterations were found to depend upon the kind and the dosage levels of the drug.

INTRODUCTION

The 20th century, with its brilliance and great technical abilities, has created an arsenal of new chemical substances that, when properly used, can improve the health and well-being of society.

These chemical agents not only provide the structural basis and energy supply of living organisms, but also regulate their functional activities. The interactions between potent chemicals and living systems contribute to the understanding of life processes and in addition provide effective methods for the treatment, prevention, and diagnosis of many diseases.

Chemical compounds used for these purposes are drugs; however these chemical inventions (drugs), when improperly used, can lead to misery and death.

One of these chemical agents is psychopharmacological or psychotropic drugs which is introduced for the treatment of mental disorders since the mid-1950 s.

During the 196O s there was a rapid expansion of psycho-pharmacological research, and many new theories of psycho-active drug effects were introduced. The clinical efficacy of many of these agents was firmly established during this decade. In recent years, emphasis has centered on biogenic amines in the CNS and their possible causal involvement in mental illness. In addition, much attention is being paid to the labilities of treatment with psychotherapeutic drugs, and a balanced view of their advantages and disadvantages is beginning to emerge (Byck, 1975).

These psychopharmacological drugs which included heterogenous group of agents; classified under the category of drugs that "selectively" modify CNS function. The agents in this group may manifest either depressant or excitatory effects. In some instances, a drug may give evidence of both effects simultaneously on different systems. Pharmacological effects of drugs from the "selective" category can be demonstrated experimently on nervous pathways that are obviously not relevant to their therapeutic action; but, nevertheless, may provide clues to those actions. Although; selectivity of drug effect may in some instant be remarkable, a drug usually affects a variety of functions of CNS in varying degree. When only one constellation of effects is wanted in a therapeutic situation, the remaining effects produced by the drug are regarded as limitations in its selectivity or by the aphorism: "one man's side effect is another man's remedy" (Esplin, 1965; 1970; Franz, 1975).

There are considerable problems in the terminology of psychoactive drugs due to the confusion in this field. The terminology applied to the various groups of psychotropic drugs is far from satisfactory.

Wade and Reynolds in 1977, defined psychotropic drugs as chemical compounds that act on the psychotic function, behaviour, or experience; they altered the mental state by affecting the neurophysiological and biochemical activity of the functional units of the CNS.

Recently, Bowman and Rand in 1980 stated that the terminology is based on a mixture of terms signifying a number of different properties, including: behavioural effect e.g. tranquilizers ; therapeutic effect e.g. antidepressant ; mode of action e.g., monoamine oxidase inhibitor; chemical structure e.g. tricyclic antidepressant ; prototype e.g. amphetamine-like. The choice of terms is arbitrary, being based partly on current trends in the literature and partly on convenience in organization of related material, but largely on personal predeliction.

The following table provides the main classes of psychotropic drugs with lists of alternative names and some examples according to Bowman and Rand, 1980.

Group name	Alternative names	Main classes	Examlples
Neuroleptics	Major tranquilizers Neuroplegics Phycholeptics Psychoplegics Antischizophrenics Antipsychotics	Phenothiazine-neuroleptics. Phenothiazine-like-neuroleptics. Butyrophenones. Diphenyl butyl-piperidines. Reserpine-like-depressants	Chlorpromazine Thioridazine F luphenazine Chlroprothixene Haloperidol Pimozide. Reserpine
Lithium salt			Lithium carbonate
Anxiolytic sedatives	Minor tranquilizers Tranquillo-sedatives Psychosedatives Ataractics Anxiolytics Antineurotic	Benzodiazepines. Carbamates Diphenylmethanes. Tetracyclic-tranquilizers.	Chlordiazepoxide Diazepam Meprobamate Benactyzine Benzoctamine

Thymoleptics	Antidepressants	Tricyclic-antidepressant.	Imipramine Amitriptyline
Monoamine oxidase inhibitors	Thymerctics Psycho-energizers Euphoriant Antidepressant.	Hydrazine-type Amphetamine-type.	Iproniazid Tranylcypromine
Psychostimulants	Psychoanaleptics Psychoactivators Psychotonics Psychomotor-stimulants. Central stimulants	Amphetamines. Amphetamine-like Stimulants. Xanthines.	Dexamphetamine Methylphenidate Caffeine

The more popular group of these psychotropic drugs is known as "Tranquilizers".

The term tranquilizer or ataractic is from the Greek ataraktos =undisturbed, undaunted was introduced in 1953 to characterized the psychotropic action of reserpine.

Now this term is a generic one and is given to a vast variety of drugs of very different types which are capable of inducing a state of calm by reducing agitation and anxiety without producing the hypnosis and clouding of consciousness typical of barbiturates or ethanol and, even if large doses of tranquilizer are given, the patient can still be aroused (Penn, 1980).

The early classification of many tranquilizers available on pharmacological basis, was a difficult task due to the lack of clinical data for many of these compounds, and to the confusion existed, even when data were available.

In 1961 Beckman classified tranquilizers according to their chemical structure to the following four principal groups:

(1) Phenothiazine derivatives
(2) Rauwolfia derivatives.
(3) Propanediol derivatives.
(4) Diphenylmethane derivatives.

The development of a new drug, chlordiazepoxide (librium) reported by Randall (1960), that did not fit chemically into any of the other tranquilizering groups was considered the beginning of a new fifth group ; later on known as benzodiazepines (WHO, 1967). This chemical classification, though imperfect yet,it was the most convenient at that time.

Recently, Wade and Reynolds in 1977 classified tranquilizers according to their clinical uses into two principal groups:

I- Neuroleptics (Major tranquilizers):

This class includes tranquilizers used mainly for the treatment of psychoses such as phenothiazines, thioxanthenes, butyrophenones and lithium carbonate.

II. Anxiolytic sedatives (Minor tranquilizers):

This class used in the treatment of psychoneuroses to reduce pathological anxiety, agitation and tension such as benzodiazepines and the propanediol carbamates (meprobamate).