DEVELOPMENTS IN PSYCHIATRY - VOLUME 1

# Modern Concepts in Psychiatric Surgery

E. R. Hitchcock, H. T. Ballantine, Jr. and B. A. Meyerson
Editors

# MODERN CONCEPTS IN PSYCHIATRIC SURGERY

Proceedings of the 5th World Congress of Psychiatric Surgery held in Boston MA, U.S.A. on August 21-25, 1978

*Editors*
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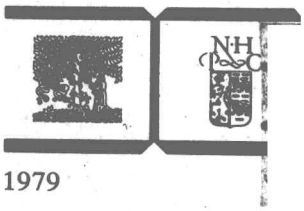

1979

ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
AMSTERDAM · NEW YORK · OXFORD

ISBN for this volume: 0-444-80108-1
ISBN for the series: 0-444-80107-3

Published by:
Elsevier/North-Holland Biomedical Press
335 Jan van Galenstraat, P.O. Box 211
Amsterdam, The Netherlands

Sole distributors for the USA and Canada:
Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

PRINTED IN THE NETHERLANDS

# PREFACE

These papers represent some of the contributions held at Pine Manor College in Brooklyn, Massachusetts, in August, 1978.

Although we were saddened by the recent death of the President, Sixto Obrador, we were steered through a successful meeting by the President of the Congress, Tom Ballantine.

The papers presented here represent the most modern concepts of psychiatric surgery and reveal the increasing awareness of the relationship between biogenic amines and ablative and stimulation surgery. Many of these papers present the findings of teams of neurosurgeons, psychiatrists, psychologists and biochemists - a trend strongly supported by the society.

The use of photo offset reproduction has meant that most authors have been responsible for their own manuscript editing. The Editors hope that for the rapidly changing field of Psychiatric Surgery the early publication made possible by this method will excuse any minor inaccuracies.

E.R.H.

# DEVELOPMENTS IN PSYCHIATRY

Volume 1 Modern Concepts in Psychiatric Surgery, edited by E.R. Hitchcock, H.T. Ballantine, Jr. and B.A. Meyerson, 1979

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# BIOCHEMICAL AND STIMULATION STUDIES

Modern Concepts in Psychiatric Surgery
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# NEUROTRANSMITTER MECHANISMS UNDERLYING PSYCHIATRIC SURGERY, ELECTROCONVULSIVE THERAPY AND ANTIDEPRESSIVE DRUG THERAPY

HOFSTATTER, L. and GIRGIS, M.

University of Missouri-Columbia, School of Medicine, Department of Psychiatry, Missouri Institute of Psychiatry, U.S.A.; & University of Sydney, Australia and University of Missouri-Columbia, same as above.

Involvement of Neurotransmitters (NT) in all treatment modalities, including Psychiatric Surgery, for psychiatric illness, particularly depressive states is implied in the title. Therefore we shall proceed to point out the essential part of the NT system in mental health and illness, the significance of NT equilibrium and disequilibrium for mental health and mental illness respectively, the equal and equalizing role of aminergic and cholinergic NTs in the maintenance of NT balance, and the paramount importance of restoration of NT balance for the therapeutic effectiveness of the three treatment modalities, particularly in depression.

Their clinically and experimentally established foundation is in sharp contrast to the originators' conception of their ingeniously conceived treatment methods, i.e. disruption of a vicious cycle of fixed cell connections in the brain by Egas Moniz (1936)[1], antagonism of epilepsy and schizophrenia by L.V. Meduna (1938)[2], and the origin of non-hypnotic ataractic psychotropic drugs from a study of histamines (1952).

Our data was derived from neuro-histochemical neuro-physiological and neuro-pharmacological investigations at the Missouri Institute of Psychiatry, U.S.A., and the University of Sydney, Australia and will enable the psychologically and biologically oriented neuro-scientist to better understand the workings of the components of his/her armamentarium.

The present investigation attempts to establish plausible and heuristic evidence of an abnormal NT imbalance with a relative predominance of acetylcholine (ACh) in some limbic structures as one of the biochemical substrates of depressive states; they

have so far commonly been attributed to underactivity or deficiency of aminergic NT according to the pioneering catecholamine hypothesis of affective disorders (Schildkraut 1965)[3]. The effective reduction of ACh and/or elevation of aminergic NT levels in these areas to reestablish normal NT equilibrium will be shown to be the common denominator, basic principle and central goal of all treatment modalities, surgical axotomy, pharmacological or electroconvulsive therapy (ECT) and available tricyclic antidepressants, responsible and essential for their success in treating depressive states.

The maintenance of a delicate self-regulating and self-correcting balance of opposing NTs within a narrow range of safety is based on their synergistic reciprocal relationship and is the condition essential for adaptive, i.e. normal emotional behavior.

This concept can be traced back to the time honored principles of constancy of the internal environment by Claude Bernard (1872), to W.B. Cannon's natural tendency toward homeostasis of bodily processes in the service of self-preservation and survival (1932), and to W.R. Hess' (1924)[4] and E. Gellhorn's (1953)[5] critical balance and synergism between ergotropic and trophotropic elements of the autonomous nervous system. They apply not only to the realm of physiology but also to that of psychiatry and were elaborated in L.V. Bertalanffy's Open System Theory of Living Systems (1966)[6] with its dynamic steady state of balanced tension and reciprocal interaction of opposing forces. Perez-Cruet, et al (1971)[7] have first presented experimental evidence of a reciprocal relationship between central cholinergic and adrenergic NTs. Marrazzi (1966)[8] stressed the relationship of excessive and nonadaptive emotional responses in mental illness and a dynamic imbalance or distorted homeostasis between excitatory and inhibitory NTs, chemical compounds that convey information between adjacent nerve cells. Janowsky (1972)[9] has laid the foundation for a bivariate cholinergic-adrenergic hypothesis of Mania and Depression, and indicated that a given affective state may represent a balance between central cholinergic and adrenergic NT activity in those areas of the brain which regulate affect. Balance among the central NT has been the subject of some recent reviews (Pradhan 1978)[10].

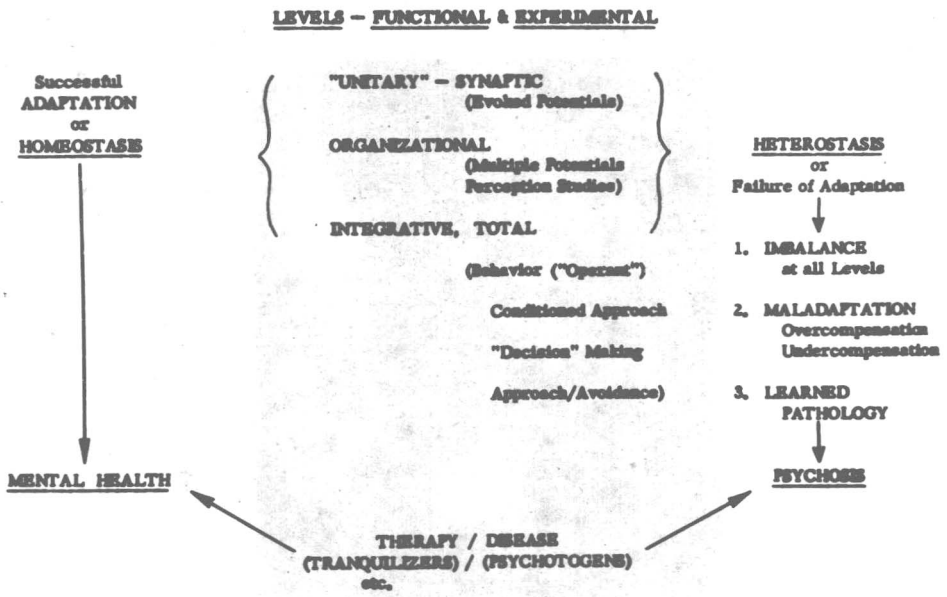


Fig. 1. Cerebral Adaptive System.
(Reproduced with permission of Dr. A. Marrazzi[8])

There is further evidence that points to specific limbic structures of the medio-orbito-temporal region and to malfunctioning neural mechanisms in that area, normally subject to cholinergic mediation as a source of disturbed behavior and a target for therapeutic intervention in psychotic depression.

Histochemical light microscopic studies with a modified Koelle's thiocholine technique (Girgis, 1967)[11] brought out a strikingly high, though uneven, concentration of acetylcholinesterase (AChE) in all relays in the "Cortical Circuits of Emotion" of Papez (1937)[12]. The limbic system ranks highest among cerebral structures in AChE content and activity throughout the animal kingdom, from rodents to primates with variation from nucleus to nucleus and from animal to animal. Invariably, however, the magno-cellular part of the amygaloid nucleus stains intensely in all mammalian brains, including the brain of man.

AChE concentration is only slight in neocortical areas, excepting moderate concentrations in the posterior orbito-frontal cortex (area 13) and the cingulate gyrus.

Fig. 2. Distribution of AChE in rabbit amygdala and other limbic structures.

The high concentration of readily available AChE in the limbic system may serve an important stabilizing and protective function in the maintenance of a more or less steady level of ACh within narrow limits of safety; it may be operative by safeguarding the physiological threshold of sensitivity of ACh and by preventing the development of pathological cholinergic hyperreactivity or hypersensitivity in susceptible neurons of the limbic system, (Hofstatter and Girgis, 1973)[12a].

Electron Histochemistry, has allowed more exact cytological localization of AChE than the light microscope (Shute and Lewis,

1965)[13].

The electron microscopic study with a modified Koelle technique (Tsuji, 1974)[14] showed AChE in the cisternae of rough endoplasmic reticulum of the perikarya of cholinergic neurons and in their nuclear envelope, with which the cisternae often communicate. Occasionally, as in the septum (The source of the cholinergic supply to the hippocampus) AChE is also present in the plasma membrane.

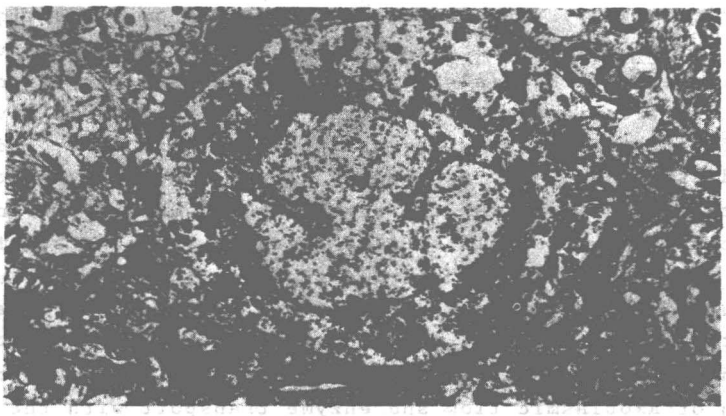

Fig. 3. Ultrastructural localization of AChE in cell bodies of Amygdala.

The Electronmicrogram of the above mentioned magno-cellular part of the basal amygdaloid nucleus shows also numerous positive synaptic endings around these cholinergic cells, suggesting both the cholinergic as well as cholinoceptive nature of a large number of its neurons.

Ultrastructural studies indicate that the enzymes needed for both synthesis and hydrolysis of the neurotransmitter are manufactured in the perikarya of the cholinergic neurons and transported in neurotubular structures in a slow but constant flow down in the axoplasm of the axon at a rate of about 20 to 400 mm/day, to be released at its terminals, the active synaptic sites, (Lewis and Hughes, 1957[15]; Haggendal, et al,

1971[16]; Lubinska, 1975[17]). There ACh is synthesized from Choline and acetate with the help of the enzyme choline-acetyl-transferase.

That transport system becomes blocked when a cholinergic nerve or axon is ligated or transected. Transitory accumulation of enzyme proximal to the lesion and disappearance of AChE distal to the lesion was demonstrated (Hughes and Lewis, 1961[18]; Eccles, 1961[19]; Pradham and Dutta, 1970[20]); the axoplasmic flow that carries the synthesizing system no longer reaches the terminals, where it is required for the generation of ACh.

This mechanism becomes readily applicable to the effect of psychiatric surgery. Any surgical procedure from the antiquated lobotomy to the modern stereotactic techniques in various topographical areas of the brain, e.g. in the medio-orbito-frontal area for the treatment of depressive states, results in severance of fiber structures in the brain, i.e. in axotomy, and thus in disruption of the axoplasmic flow. The supply of the raw materials necessary for the synthesis of ACh, is prevented from reaching the terminals at some distance from the surgical target. Thus synthesis and storage of excessive ACh in the area responsible for abnormal behavior is reduced. Absence of regeneration in the central nervous system renders the discontinuation of the transected fibers permanent. The resulting cessation of axoplasmic flow and enzyme transport with the consequent reduction of excessive ACh synthesis and store contributes to the enduring effect of axotomy, i.e. psychiatric surgery through restoration of NT balance.

Electroconvulsive therapy for psychotic depression has been accepted for its therapeutic efficacy, rapidity, and superiority of outcome. It is brought about in a small series of bilateral or unilateral non-dominant application of alternating electric current at the temples. It is administered 2-3 times per week with precautionary measures, such as positioning of the patient in hyperextension of the spine, i.v. thiopental or methohexital anesthesia, blockade of the inconsequential motor component of the convulsions by muscle relaxants like succinyl-choline (Anectine), and by hyperoxygenation. It exerts its effect through the cerebral component, however, i.e. a multitude of wide spread biochemical concomitants, among them the chemical processes induced on the neuroregulatory system, stirring both the biogenic amines and the cholinergic and ACh system in an

apparent effort to re-establish equilibrium and restore the situation toward normal. The mobilization of the ACh system by ECT is reflected in the immediate, though not persistent effect of single seizures on the ACh content of the brain and its depletion into the cerebrospinal fluid (CSF). The levels of bound and free ACh in the brain increase significantly during the seizure itself, postictally, particularly after a series of seizures, however, both, more so the free ACh, decrease gradually because of the increased synthesis and turnover (Karczmar, 1974[21]), saturation and blockage of cholinergic receptors (Goldberg, et al, 1976)[22], and the appearance of considerable amounts of cholin and ACh in the cerebrospinal fluid (CSF) (Fink, 1966[23]; Essman, 1972[24]). Increased release of ACh from many cortical and subcortical areas of the brain into extracellular space, cerebral ventricle, and the cerebrospinal fluid is a general, non persisting corollary of convulsions whether induced by head trauma, epilepsy, ECS, or chemical agents like the inhalant flurothyl (indoklone), or I.V. pentylenetetrazole, i.e. metrazole (Bornstein, 1946[25]; Tower and MacEachern, 1948[26]; Fink, 1966[23]). ACh was also collected from the CSF of persons who had died after generalized convulsions (Hitchcock, 1968)[27].

The prompt adaptive responsiveness of the ACh system to repeated ECT is shared by the biogenic amines, with their persistent alteration of metabolism, in the direction of increased synthesis, release, turnover, and concentration of serotonin (Kety, et al, 1967[28]), dopamine (Engel, et al, 1968[29]; Billiet, et al, 1970[30]), and nor-ephedrine (Kety, et al, 1967[28]; Ladisch, Steinhauff, & Matussek, 1969[31]; Schildkraut & Draskoczy, 1974[32]). They participate effectively in the destabilization of the neurotransmitter disequilibrium with their newly elevated level of availability and functioning; they seem to contribute to the establishment of a new neurotransmitter balance that may vary in different people (Barchas, et al, 1978)[33]. The reestablished physiological synergism of cholinergic and aminergic neurotransmitters may account for the restoration of normal emotional life by ECT in the previously severely and/or suicidal depressed patient.

TRICYCLIC ANTIDEPRESSANTS.

The psychopharmacology of depression, including biochemical subtypes, of the past has ever since 1957 focussed mainly on

functional underactivity or deficiency of biogenic amines and adhered to the univariate catecholamine or norepinephrine and serotonine hypothesis (Bunney, 1978)[34]. Therefore, antidepressive drugs, thymoleptics, capable of elevating the level of available biogenic amine concentration in the synaptic gap at the receptor came into general use. Some, like mono-amine-oxydase inhibitors would counteract their metabolic breakdown, others like the more effective tricyclics, would block their re-uptake into the presynaptic neuron that released them into the synaptic cleft. The beneficial effect of administering tryptophane, a precursor of the aminergic neurotransmitter serotonin, to patients with depression support the generally accepted hypothesis.

On the other hand, the anti-depressant activity of certain anticholinergic drugs (Feldberg & Sherwood, 1955)[35] and the anticholinergic "side" effects of the important antidepressant tricyclic drugs suggest some role of the ACh system in clinical depression and in the beneficial effects of antidepressant drugs (Kety, 1974)[36]. The precipitation of depression by CHE inhibitors that increase the available level of ACh in the brain, be it by accidental poisoning with cholinesterase inhibitor insecticides and poisoning with nerve gasses, or by experimental administration of physostigmine to manic patients (Janowsky, et al, 1972)[9] are compelling evidence for the important part of an elevated ACh level in the biochemistry of depression.

Both the aminergic and the cholinergic system seem to have their share in producing the neurotransmitter disequilibrium, necessary and responsible for emotional dysfunction in depression; the pathological shift in the physiological balance of opposing though normally synergistic neurotransmitter systems represents a tipping of the scale--in favor of ACh, to which both systems apparently may contribute by overfunction or underfunction, respectively.

Restoration of neurotransmitter balance and recovery from emotional depression requires either considerable alteration of one or the other, or both mutually reinforcing transmitter system, i.e. diminution or increase respectively, or a simultaneous moderation of both systems as well exemplified in Parkinson's Disease. The presently available antidepressant