HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. REMOND

VOLUME 7

Physiological Correlates of EEG

EDITORS: E. K. KILLAM AND K. KILLAM

Department of Pharmacology, School of Medicine, University of California at Davis, Davis, Calif. (U.S.A.)

PART C

Effect of Drugs on the EEG

EDITOR: V. G. LONGO

Istituto Superiore di Sanità, Rome (Italy)

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International Federation of Societies for EEG and Clinical Neurophysiology

A great need has long been felt for a Handbook giving a complete picture of the present-day knowledge on the electrical activity of the nervous system.

The International Federation of Societies for EEG and Clinical Neurophysiology is happy to be able to present such a Handbook, of which this is a small part.

The decision to prepare this work was made formally by the Federation at its VIIth International Congress. Since then nearly two hundred specialists from all over the world have collaborated in writing the Handbook, each part being prepared jointly by a team of writers.

The Handbook begins with an appraisal of 40 years of achievements by pioneers in these fields and an evaluation of the current use and future perspectives of EEG and EMG. The work subsequently progresses through a wide variety of topics—for example, an analysis of the basic principles of the electrogenesis of the nervous system; a critical review of techniques and methods, including data processing; a description of the normal EEG from birth to death, with special consideration of the effect of physiological and metabolic variables and of the changes relative to brain function and the individual's behaviour in his environment. Finally, a large clinical section covering the electrical abnormalities in various diseases is introduced by a study of electrographic semeiology and of the rules of diagnostic interpretation.

The Handbook will be published in 16 volumes comprising 40 parts (about 2500 pages altogether). For speed of publication most of the 40 parts will be published separately and in random order.

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Introduction

This volume explores the relationships between electroencephalographic (EEG) changes induced by drugs and the mechanism of action or use of particular drugs. The introductory comments are offered to lend some perspective to the individual Sections.

The effects of drugs upon the EEG of both man and animals may be described in relation to normative values for that species. In some instances, normative values may be from the non-drug state. However, in man there may be other drugs present as part of a therapeutic regimen or drug-taking pattern. The normative values include, in addition to the baseline drug state, neurological, psychological and biochemical factors.

As is well known, each neuroanatomical site has a catalog of values that can describe the brain waves from that site. Amplitude and frequency characteristics of voltage gradients are the usual parameters quantified. There are infradien and circadian cycles wherein the descriptors of brain activity may be correlated with the combined chemical, physiological and psychological state of the individual. Segments or epochs of brain wave activity selected from these cyclical states will vary in their precise mathematical description with the species. In the rat, rabbit, cat and dog it is not possible with computer quantification of the EEG to describe clinical parameters such as alpha activity, beta activity, etc. However, trained investigators can classify EEGs from these species into stages describing the characteristics of the sleep–wakefulness continuum for that species. Further, such data supported by other physiological variables may be rigorously descriptive to allow discrimination of all subtle changes produced by drugs.

With subhuman primates and man, computer analysis of epochs of brain waves permits recognition of standing frequencies that fall into the classical clinical indicators. The use of other analyses such as spectral parameters can yield an even more useful description of drug effects. Such descriptions, on the one hand, may have therapeutic importance as monitors of the shifting pharmacodynamics of drugs administered chronically, or, on the other hand, may serve as a framework for future research efforts focused on the mechanism of action of the drug and/or an explanation of the underlying biological state.

As indicated above in the absence of drugs and pathology, each brain site will have characteristic brain activity that correlates and fluctuates with the behavioral state. Following the administration of drugs, one may observe a new set of descriptors characterizing the brain waves from particular brain sites. This may take the form of new frequency components or mixtures thereof. Or it may take the form of spike discharges or other abnormalities not seen in the resting, non-drug condition.

A second class of drug-induced changes would be an uncoupling of brain activity from the observable behavior. The usual example cited is the sleep-like EEG seen following atropine even though there is no apparent depression of spontaneous behavior. However, detailed analysis of these changes suggest that the "uncoupling" effect should more appropriately be recognized as the hallucinatory state induced with atropine or at least as a descriptor of a dissociative effect on behavior. This illustrates the progress made from attempts at simplistic correlations to specific analytical dissection of the relation of EEG to brain function.

A third general effect seen following drugs may be considered as stabilizing of brain wave activity. In the non-drug state, serial characterizations reveal that the infradien cyclicity has modes, duration, and in some instances, specific sequencing. Following some drugs, these characteristics of infradien cyclicity disappear or become fixed in one mode. These stabilized periods may either parallel or be divergent from the ongoing behavior of the subject. EEG changes following amphetamine or physostigmine are examples.

The aforegoing are some of the changes that may be observed in the intact subject. Other experimental preparations have been used in animals either to explore the mechanism of action of a particular drug or to define more precisely the drug's spectrum of activity. Such preparations include lesioned subjects, immobilized subjects, subjects with genetic variations expressed by neurological abnormalities and anesthetized subjects. The lesioned subject is most often used to limit the neurological framework upon which drug effects would be evaluated. Other lesions, however, may be used to induce abnormal firing of neurons to simulate a particular syndrome. In these preparations the drugs may alter the initiation or the propagation of the abnormal activity. This may occur with alteration of attendant behavioral states. Still other lesions may be used to disrupt selectively modulatory processes. The resultant may be altered CNS function without the induction of frank abnormal activity.

The use of immobilized subjects has received criticism which reflects more upon an unevenness in training and scientific standards than on the validity of the preparation. The use of immobilizing agents eliminates *motor expression* of behavior, of drug effects and of concomitant changes. Simply because the subject cannot respond motorically does not relieve the investigator from the responsibility to monitor multiple events to assess the consequences of physical and chemical manipulations. With these preparations the subject is prepared including the installation of monitoring pickups under a short-acting general anesthetic, usually a volatile substance. The subject is then immobilized with a neuromuscular blocking drug. Full physiological support is instituted while the subject recovers from the anesthetic and throughout the period of data collection.

The use of subjects with genetic abnormalities presents other challenges. In order to allow maximal usefulness of the data derived from such preparations the nature of the abnormality must be characterized. Normative data from other members of the species are invaluable. Drug studies may be used to dissect the abnormality. Other substances may be evaluated as therapy for the specific syndrome. In some

instances the genetic abnormality may be expressed only in a specific age group. Thus, the developmental aspects of EEG characteristics for that species become important. Drug effects may then interact with the processes of maturation and the specific cyclicity of the genetic syndrome.

The use of anesthetized subjects has been the classical approach in neurophysiology. It is not surprising that drug evaluation has recapitulated scientific phylogeny. One continues to see reports on the effects of LSD-25 in anesthetized animals with extrapolations to the hallucinatory effects of this drug in man. However, the controlled combinatorial use of drugs in the operating room is common practice. The complexities of correlating the amnestic effects of a given concoction with EEG changes are formidable. Clinical neuropharmacology in this setting is always a compromise between producing the desired preparation for the surgeon and gathering fundamental information to further the therapeutic use of particular drugs or mixtures.

In addition to the use of subjects with genetic abnormalities to model disease such as epilepsy, a variety of drugs are used to precipitate abnormal discharges. These ictal periods may undergo modification following drugs in terms of alterations in the motor expression of the seizure and for modification of the EEG sequelae. In many instances it is more parsimonious to describe the anticonvulsant effect in terms of altering the motor signs. Thus, the control of the seizure becomes primary; and the EEG sequelae, secondary.

Up to this point, the discussion has centered on the acute exposure of individuals to drug(s). With continued or chronic administration of drugs other factors become involved which may influence EEG signs. To some extent all drugs produce tolerance, *i.e.*, with repeated administration, the pharmacologically induced events may change or decrease in severity. The new descriptors may stabilize. Then, the sudden collapse of the tolerant state by the use of antagonists or simply the termination of the administration schedule will precipitate behavioral, neurological and EEG changes that were not present beforehand. The nature of the tolerant state and the consequences of abrupt termination of that state is dependent on the class of drug(s) used. Further, the duration of the withdrawal syndrome will depend upon the pharmacokinetics of the drugs. Often the serial monitoring of EEG signs will predict the return to relative normalcy and evaluate the success of supportive therapy.

The final area of concern in this introduction is the applicability or translation of pharmacological findings from animals to man and *vice versa*. There is no argument that direct translation of results is a rarity. However, the fundamental concepts and principles are generalizable. The effects of drugs in all species are continua of pharmacological changes, rather than discrete events. Thus, one studies the sedative properties of drug X in animals and man over that dose *range* appropriate for that species. The fact that the absolute ranges do not overlap across species is a triviality. Stated another way, the pharmacokinetics of drugs contribute more to the differences in dose ranges across species than the responses of the target systems. To be sure, there are syndromes that to date appear to be unique to man. Animal models of these disease states may be useful in narrowing the field of possible therapeutic agents. The other strategy that continues is the serendipitous discovery of a therapy

in man. Then, the phenomenon is taken back to the animal subject to dissect the efficacious aspects. New or more productive approaches or understanding may emerge.

Section I. EEG Effects of Cholinergic and Anticholinergic Drugs

INTRODUCTION

Acetylcholine (ACh) and many agents which modify its action or alter its rate of destruction have profound effects on central nervous function, with corresponding repercussions in the EEG. The distribution of ACh as well as related enzymatic systems (choline-acetylase, acetyl-cholinesterase) has been thoroughly described. The dissociation between EEG and behavior by drugs interfering with cholinergic synapses raised important questions about the correlation of the electro-physiological events. These and others are the reasons why so much attention has been paid to the central effects of drugs affecting cholinergic transmission.

Exploration on the various cholinergic sites in the central nervous system (CNS) has followed the same lines of investigation and has used the same drugs as for ganglionic and neuromuscular transmission. Extreme difficulties are, however, involved in recognizing the functions of ACh and related drugs in the CNS, as compared with peripheral sites, because of the structural complexity of cerebral organization.

A. EFFECTS OF CHOLINERGIC DRUGS IN ANIMALS

1. Acetylcholine

Early experimental work on ACh involved topical application to the exposed cortex. In concentrations of 0.2–1 % ACh evokes a desynchronization or a flattening of the EEG in the rabbit (Moruzzi 1939) and in the cat (Miller *et al.* 1940). Higher concentrations (up to 10–15 %) also induce appearance of bursts of spikes eventually leading to a "grand mal" seizure. Acetyl-β-methylcholine (1.25 %) and carbamylmethylcholine (0.13 %) have similar effects. The application of physostigmine (1 %) on the motor cortex of the rabbit induces a flattening and a desynchronization of the EEG, and clonic movements of the head. Physostigmine followed by ACh (1–5 %) induces a discharge made up of grouped spikes, once again leading to a "grand mal" seizure. Spasms and tonico-clonic movements of the muzzle characterize the motor equivalent of the electrical seizure. Atropine or scopolamine, administered i.v., block the action of topical physostigmine, or ACh, or both (Miller *et al.* 1940; Brenner and Merritt 1942; Chatfield and Dempsey 1942; Funderburk and Case 1951; Longo 1962).

When ACh is administered intravenously its penetration into the CNS is poor. ACh was at first thought to be a convulsant in rabbits (Rossi 1939) or cats (Brenner

and Merritt 1942). A few seconds after the i.v. administration of ACh (50–75 μg/kg) to the rabbit, irregular high voltage (400–600 μV) low frequency (1.5–3 c/sec) waves appear in the record. These patterns last for a few seconds, and the slowing of the EEG always corresponds to the drop in blood pressure (Longo 1962). EEG and behavioral changes that usually occur after intravenous ACh are probably due to circulatory collapse rather than to a direct effect on the brain (*cf.* Williams 1941; Nakao *et al.* 1956).

Small amounts of ACh injected in the rabbit (0.5–2 μg/*toto*) *via* the internal carotid artery produce a motor response (ranging from torsion of the neck to an escape reaction) and a desynchronization of the EEG, similar to the arousal reaction induced by external stimuli. In the *cerveau isolé* rabbit 1–2 μg of ACh has no effect, while doses ranging from 5 to 10 μg induce discharges of high voltage waves, at a frequency of 7–10 c/sec. Pre-treatment with atropine (1–3 mg/kg i.v.) or scopolamine (0.1–0.2 mg/kg) abolishes the EEG response, but not the motor reaction (Longo and Silvestrini 1957a; Yamamoto and Domino 1967).

2. *Arecoline and pilocarpine*

Brief desynchronization in the cortex and synchronization in the hippocampus and subcortex occur after arecoline (0.01–0.08 mg/kg i.v.) (Herz 1963a). Similar results are described by Domino *et al.* (1968) in the cat (see also Domino 1967; Yamamoto and Domino 1967).

Pilocarpine (0.15 mg/kg i.v.) produces prompt EEG activation in neocortical and limbic systems as well as a behavioral arousal in the cat. Pilocarpine-induced EEG activation is blocked completely by atropine; it is also markedly reduced by pre-treatment with methyl atropine (a quaternary derivate which allegedly does not cross the blood–brain barrier) and is enhanced by mecamylamine (Domino *et al.* 1968). Oxotremorine-induced EEG activation (0.3 mg/kg i.v.) is partially antagonized by scopolamine or by trihexyphenidyl (Ban and Hojo 1971).

3. *Anticholinesterase agents*

Physostigmine and non-quaternary organophosphates injected systemically, induce EEG desynchronization as well as inhibition of cortical recruitment by thalamic or caudate stimulation in cats (Funderburk and Case 1951; Bradley and Elkes 1953b; Rothballer *et al.* 1961) and rabbits (Longo and Silvestrini 1957b; Stumpf 1965a, b). EEG and behavioral "grand mal" patterns may also appear, particularly if the drugs are administered intracarotid (Longo *et al.* 1960b) or by direct microinjections into the hippocampus (Baker and Benedict 1968). Similar effects have been shown for diisopropylfluorophosphate (DFP; Wescoe *et al.* 1948), parathion (Duesing and Erdman 1954) and isopropoxymethylphosphoryl fluoride (sarin; Longo *et al.* 1960b) (Fig. 1).

Neostigmine and other quaternary compounds do not have noticeable effects on

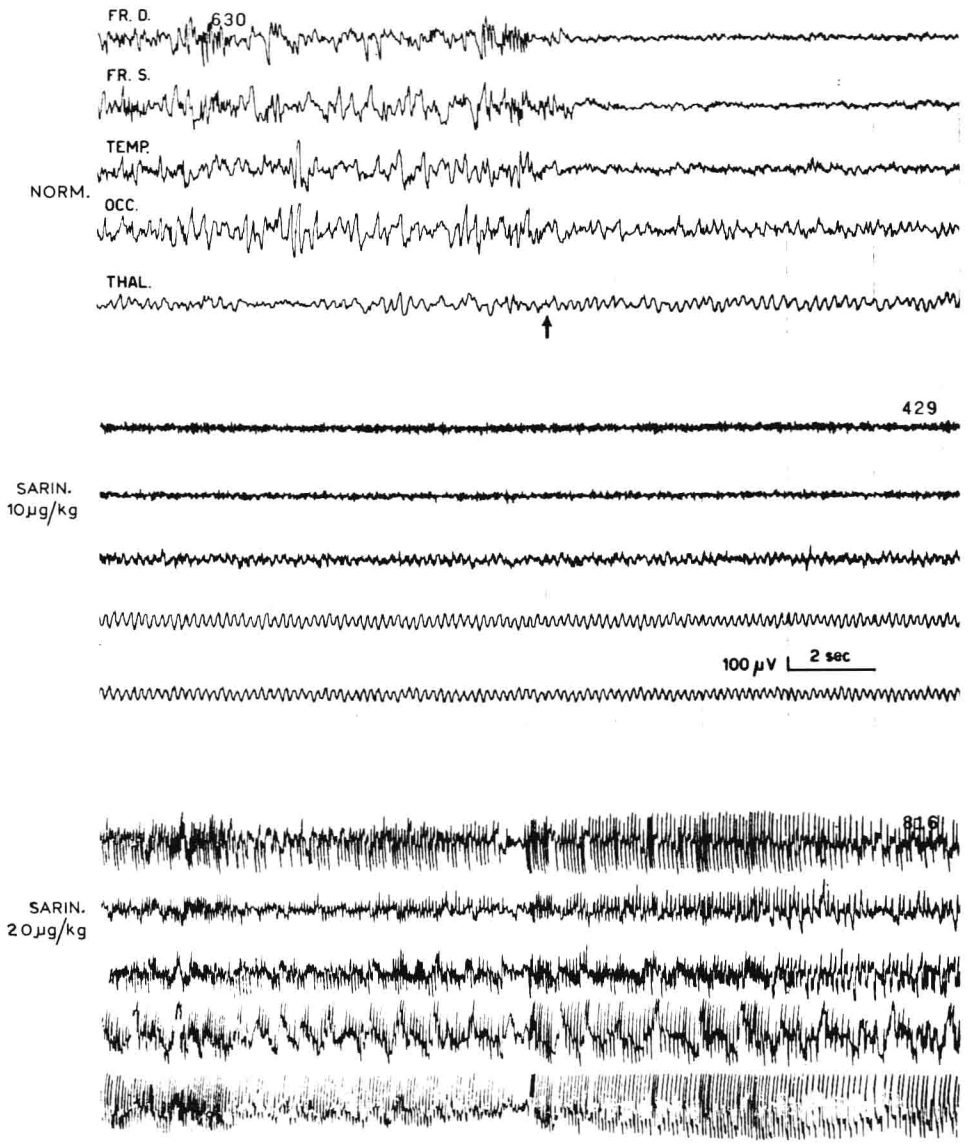

Fig. 1. Effect of sarin on the EEG of the curarized rabbit. The normal record is replaced by an activated tracing following the administration of 10 μg/kg of sarin. Twenty μg/kg bring about a grand mal attack. *Leads:* FR.D., R anterior sensorimotor cortex; FR.S., L anterior sensorimotor cortex; TEMP., L associative cortex–R associative cortex; OCC., L optic cortex–R optic cortex; THAL., anteromedial nuclei of the thalamus. (From Longo *et al.* 1960b)

the EEG. This is probably due to the blood–brain barrier, which prevents the penetration of anticholinesterase quaternary compounds into the brain (Schweitzer and Wright 1937; Koelle and Steiner 1956). However, neostigmine applied locally on the cortex induces the same potentiating effects as physostigmine on the convulsant action of locally applied ACh (Chatfield and Dempsey 1942).