PHARMACOLOGY OF THE CENTRAL CHOLINERGIC SYNAPSES[1]

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The concept that acetylcholine (ACh) may play a significant role in the central nervous system (CNS) was suggested by Dale (1) shortly after the discovery of its transmission of nerve signals across certain peripheral synapses. The direct experimental proof of this idea, however, has been very vague despite a large quantity of indirect proofs, summarized in several reviews (2–6).

In the past year, the evidence of the cholinergic structures in the CNS has been supported by many new results yielded by different experimental approaches. Considering the limited extent of this review, only the pharmacological approach has been included.

Effect of Drugs on the Level and Localization of Acetylcholine in the Central Nervous System

Many authors have struggled to determine the level of ACh in the CNS as a whole or in its different parts, and the effect of drugs on these levels. ACh was tested by biological methods, using the isolated frog rectus abdominis muscle, guinea pig ileum, longitudinal strip of the leech dorsal muscle, or the blood pressure change of an eviscerated cat. Recently, the methods for the analytic determination of ACh by gas chromatography (15) or polarography (18) have been elaborated. Table I shows the level of ACh in the rat brain according to different authors.

Cholinolytic drugs acting on the behavior of experimental animals decrease the levels of ACh according to their central activity (9–12, 14). The most effective is scopolamine, followed by benactyzine and atropine. There are great differences in the levels of ACh in different parts of the brain; the highest values are found in basal ganglia and the mesencephalon; the lowest in the cerebellum and the cortex (10, 12). Decrease of ACh caused by cholinolytics is about the same in all parts of the brain (10) (Table II). However, a relatively lower shift has been observed in the tissues rich in ACh (i.e., basal ganglia and mesencephalon). In further studies it was established that also two other agents, psychotomimetic in man and studied by Abood, JB-336 and JB-8099, produced in rats a reduction in brain ACh comparable to that found with scopolamine and atropine. Two other similar compounds, without psychotomimetic activity, caused no change in brain ACh (19).

[1] The survey of the literature pertaining to this review was concluded June 1, 1966.

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TABLE I

LEVEL OF ACETYLCHOLINE IN THE RAT BRAIN ACCORDING TO THE DIFFERENT AUTHORS

Authors	μg/g of fresh tissue
Bose & Gupta (7)	3.38 ±0.49
Bose, Saifi & Sharma (8)	2.38 ±0.18 2.67 ±0.17
Fink (9)	2.984±0.065
Fink & Urban (10)	2.984±0.065
Giarman & Pepeu (11)	2.95 ±0.18
Giarman & Pepeu (12)	2.87 ±0.26
Herken & Neubert (13)	2.43 ±0.15
Holmstedt, Lundgren & Sundwall (14)	2.534
Stavinoha & Ryan (15)	2.65 ±0.11 (guinea pig ileum) 3.81 ±0.09 (gas chromatograph)
Tobias, Lipton & Lepinat (16)	2.9
Torda & Wolf (17)	3.7

It was concluded that among certain cholinolytic psychotomimetic derivatives the psychotomimetic effects are linked with an alteration in the metabolism of ACh in the brain. The most likely mechanism seems to be that these drugs alter storage sites of ACh in a manner leading to reduced uptake of newly synthesized ACh or increased release of ACh from bound form, or both. In agreement with these findings, drugs stimulating the CNS, e.g., tremorine and oxotremorine (14, 20), increase the level of ACh in the CNS. The analgesic effect of morphine and the development of morphine tolerance and abstinence symptoms are not causally connected with the level of ACh in the brain (22, 23).

Together with the lowering of the ACh level in the brain, the output of ACh from the cortex of the cat is increased after intravenous administration of 1 mg/kg of atropine sulfate, while atropine methylbromide given in the same dosage is 10 to 20 times less effective (24). It was concluded that atropine increases ACh output by a direct action on the area of ACh release, in-

TABLE II

THE INFLUENCE OF ATROPINE AND BENACTYZINE ON THE LEVELS OF THE ACETYLCHOLINE-LIKE SUBSTANCES IN THE DIFFERENT PARTS OF THE BRAIN OF RATS (ACH μg/g FRESH TISSUE) (10)

Part of brain	Controls ($n=18$)	Atropine, 5% LD_{50} (21.05 mg/kg IM) 30 min. ($n=14$)	Benactyzine, 5% LD_{50} (7.36 mg/kg IM) 30 min. ($n=8$)
1 Cortex	2.195±0.598	2.083±0.453	1.549±0.281
2 GG basalia	4.073±0.653	3.063±0.726	3.221±0.552
3 Mesencephalon	3.864±0.550	3.077±0.462	3.341±0.479
4 Cerebellum	1.360±0.601	1.304±0.370	0.710±0.133
5 Medulla oblongata	2.471±0.573	2.531±0.639	2.455±0.449
Average for the complete brain from values 1–5	2.793±1.169	2.412±0.855	2.255±1.088
Control values for the complete brain	2.984±0.065	—	—

dependently of EEG effects, and that the site on which cholinergic blocking agents act to increase ACh output is more accessible from the blood stream than the site responsible for the EEG effects. However, the exact mechanism by which atropine increases ACh output was not established.

General anesthetics (Na-pentobarbital, ether, ethychloride) increase the ACh level in the brain according to the depth of the narcosis (25, 26), whereas analeptics (pentylentetrazol, picrotoxin) decrease this level (21, 25).

DIRECT ADMINISTRATION OF CHOLINERGIC DRUGS INTO THE CNS

After the administration into the blood circulation, the effect of drugs on the CNS depends on three important factors: degradation, peripheral autonomic effect, and penetration through the blood-brain barrier. To eliminate these factors, several methods have been elaborated for the direct administration of the drugs close to or into the central nervous system. Despite important progress in these techniques in the last few years, the experiments are still far from the physiological conditions. Nevertheless, they have furthered the understanding of the effect of neurotropic drugs.

Administration of drugs into the cerebral ventricles or tissue by implanted cannulas.—An important advance in the technique for studying the central nervous system pharmacologically has apparently been furnished by the recent work of Grossman (27). This investigator has developed a method for the measurement of both cholinergic and adrenergic activities in one part of the brain. The method is based on the finding that different and specific behavior can be elicited by direct application of cholinergic or adrenergic substances into the hypothalamus of the rat.

A double-cannula system, consisting of two concentrically mounted syringe needles, is permanently implanted in a region of the hypothalamus that regulates the intake of food and water. Minute amounts of crystalline chemicals are deposited at the selected site by placing them on the tip of the removable inner cannula before reinserting it.

Applying this method, Grossman (27) found that ACh (capped by physostigmine) or carbachol introduced through the cannula caused water-saturated rats to drink, whereas norepinephrine and epinephrine caused food-saturated rats to eat. Grossman concluded from these results that a hypothalamic drinking mechanism is selectively activated by cholinergic stimulation, whereas a hypothalamic feeding mechanism is activitated by adrenergic stimulation. Because both effects were obtained by introducing the appropriate chemicals through the same cannula, it may be assumed that the cell concentrations involved in the two forms of behavior lie in close proximity.

Recently, Grossman (28, 29) extended these experiments to other structures, e.g., the ventral amygdala. He stated that this area was also very sensitive to the cholinergic drugs (ACh, carbachol, and dimethylaminoethanol) and that atropine injected intraperitoneally blocked these effects.

Stein (30) continued this research of the cholinergic structures in the hypothalamus of the rat, and compared atropine and scopolamine with their centrally inactive quaternary analogues, atropine methylnitrate and scopolamine methylnitrate, for the effects on water and food intake. All drugs inhibited eating, but only the centrally active compounds (with tertiary nitrogen) inhibited drinking.

Together with Seifter (31) Stein demonstrated further that this central cholinergic effect was based on a muscarinic, and not on a nicotinic action. Muscarine had an effect equal to carbachol; strong drinking was elicited within five to ten minutes and persisted for almost an hour. Nicotine had only a weak, apparently nonspecific effect.

Administration of drugs by microelectrophoretic technique.—The most important progress in the study of "direct" effect of drugs upon the CNS has been the elaboration of the local administration of drugs by means of electrophoresis through multibarreled micropipettes. This method, developed by Curtis & Eccles in 1958, has now been used in many laboratories and has brought much new, interesting knowledge.

The microelectrophoretic technique of testing substances consists of the injection of ions by electrical currents from one or more barrels of a multibarreled micropipette while extra- or intracellular records of the electrical activity of a single neuron are being obtained (32).

The neuron can be identified by its position within the nervous system and by its responses to synaptic and antidromic stimulation. As many as six extracellularly located micropipettes can be used for drug administration while the extracellular spike potentials are simultaneously recorded.

By use of the electrophoretic technique, ACh has been shown to be excitant of neurons in the spinal cord (33–36), medulla oblongata (37, 38), hypothalamus (39), olfactory bulb neurons (40), midbrain (41, 42), thalamus

TABLE III

ACTION OF CHOLINOMIMETICS UPON RECEPTORS IN CNS[a] (MICROELECTROPHORETIC TECHNIQUE) (47)

Substance	Central receptors		
	Cortex	Thalamus	Renshaw cells
Acetylcholine	++	++	++
Acetyl-β-methylcholine	+++	+	+
Carbamylcholine	+	+++	+++
DL-muscarine	+++	+	+
Nicotine	±	+	+++

[a] Potencies relative to that of acetylcholine.

(43), and cerebral cortex (44, 45). However, many other neurons are insensitive to electrophoretically administered ACh and it is clear that this compound is not the only transmitter within the feline CNS.

Table III shows the relative sensitivity of the nervous receptors in the cortex, thalamus, and Renshaw cells, i.e., the cells located in the ventromedical part of the ventral horn of the feline spinal cord, to the administration of ACh, acetyl-β-methylcholine, carbamylcholine, DL-muscarine, and nicotine (46). According to this sensitivity it seems that the cortex receptors behave as "muscarinic," the Renshaw cells as "nicotinic," and the thalamus receptors as both. In the midbrain, about 35 per cent of the neurons reacted to the ACh administration by excitation, 12 per cent by inhibition, and the rest of the cells did not respond. Nicotine evoked only excitation (43).

From the results obtained it was possible to conclude that there is now evidence of acetylcholine-sensitive neurons within various regions of the mammalian central nervous system, and the presence of receptors for ACh is almost certainly related to the role of this substance as a synaptic transmitter. The term "nicotinic" and "muscarinic," which were originally introduced to describe peripheral acetylcholine receptors (47) and later suggested even for receptors in the CNS (48), can be applied in a general fashion to some of these central receptors.

EFFECT OF CHOLINOMIMETIC AND ANTICHOLINERGIC DRUGS ON CONDITIONING, LEARNING, AND RETENTION

Natural drugs acting on the central cholinergic system have been used and abused for many years as remedies, stimulants, or hallucinogens. However, the mode of their action on the psychic functions have been studied only recently. The papers dealing with this problem are too numerous to permit me to mention all of them in this short review. Therefore, the main and recent papers have been summarized in the Tables IV, V, and VI accord-

TABLE IV

STUDIES OF THE EFFECT OF CHOLINOMIMETIC DRUGS ON CONDITIONING, LEARNING, AND RETENTION OF EXPERIMENTAL ANIMALS

Drug	Animal	Dose mg/kg	Administration	References
Arecoline	Rat	2.0	subcutaneous	49
	Rat	0.5, 1.0, 2.0	subcutaneous	50
	Mouse	0.2–2.0	subcutaneous	51
Physostigmine	Rat	0.5	intraperitoneal	52
	Rat	0.16–1.28	intraperitoneal	53
	Rat	0.25	subcutaneous	49
	Rat	0.5	intraperitoneal	54
	Rat	0.1, 0.5	intraperitoneal	55
	Rat	0.25–0.75	intraperitoneal	56
Nicotine	Rat	0.02	subcutaneous	57
	Rat	0.1, 0.2	intraperitoneal	58
	Rat	0.05–0.1	subcutaneous	59
	Rat	0.5–2.5	subcutaneous	60
	Rat	0.05, 0.2, 1.0	intraperitoneal	61
	Rabbit	0.1, 0.2	intravenous	51
	Dog	0.02–0.2	subcutaneous	62
Tremorine	Rat	5.0, 10.0, 20.0	subcutaneous	50

ing to the drug, species of animal used, the dose of the drug, and type of administration.

All authors of these papers have stressed the difficulties in the research in this field, originating from the individual differences in the reactions of the animal even of the same age, breed, and sex, and from the technique and dose used. Sometimes entirely opposite reactions to the same drug and the same dose would occur according to the different CNS excitability of the animals (55, 56, 63, 94, 95).

It is very interesting to note that the change in the behavior of the animals is, at certain dose levels, similar after the administration of cholinomimetic or anticholinergic drugs, although in a combination there is the mutual antagonism of these effects and the EEG patterns are rather different.

The spontaneous activity of the laboratory animals is enhanced and resembles the orienting activity; these movements are, however, without aim (55, 95).

The penetration through the blood-brain barrier is another important factor in the central effect of cholinergic drugs. Quaternary ammonium bases, although their affinity to the cholinergic receptors is rather high, do

TABLE V

STUDIES OF THE EFFECT OF ANTICHOLINERGIC DRUGS ON CONDITIONING, LEARNING, AND RETENTION IN THE EXPERIMENTAL ANIMALS

Drug	Animal	Dose mg/kg	Administration	References
Atropine	Rat	8.0	subcutaneous	63
	Rat	6.0	intraperitoneal	64
	Rat	20.0	subcutaneous	65
	Rat	2.0, 5.0	intraperitoneal	55
	Rat	1.0–20.0	intraperitoneal	66
	Rat	1.0, 5.0	intraperitoneal	67
	Rat	5.0	intraperitoneal	68
	Rat	2.0	intraperitoneal	69
	Dog	0.17–0.5	subcutaneous	70
	Mouse	30.0–60.0	subcutaneous	70
	Rabbit	0.5	intravenous	71
	Monkey	0.1, 0.3, 1.0	intravenous	72
	Monkey	0.5, 1.3	subcutaneous	73
Scopolamine	Rat	0.6	intramuscular	74
	Rat	0.1–2.0	subcutaneous	75
	Rat	0.1, 1.0	subcutaneous	76
	Rat	1.0	subcutaneous	77
	Rat	0.05–0.4	intraperitoneal	78
	Rat	0.1	subcutaneous	63
	Rat	0.1–0.8	subcutaneous	79
	Rat	0.5	intraperitoneal	80
	Rat	0.1	subcutaneous	65
	Rat	0.13, 1.05	subcutaneous	81
	Rabbit	0.025, 0.05	intravenous	71
	Rabbit	0.1	intravenous	82
	Monkey	0.01–0.1	intramuscular	83
	Monkey	0.01–0.1	intravenous	72
l-Hyoscyamine	Rat	1.0, 8.0	subcutaneous	81
Benactyzine	Rat	0.5–10.0	subcutaneous	84, 85, 86
	Rat	0.1–8.0	intraperitoneal	87
	Cat	0.75–5.0	subcutaneous	88
JB-329	Monkey	4.0–5.0	intramuscular	89
	Dog	0.5–1.0	intravenous	90
Ditran	Dog	0.5	intravenous	91
Phencyclidine	Rat	0.2–0.6	subcutaneous	92, 93

TABLE VI

EFFECT OF CHOLINOMIMETIC DRUGS ON THE ELECTROENCEPHALOGRAM OF THE EXPERIMENTAL ANIMALS

Drug	Animal	Dose mg/kg	Administration	References
Acetylcholine	Cat	1% sol.	Topic	107
	Cat	1%–10% sol.	Topic	108
	Cat	10.0–25.0	intracisternal	109
	Cat	0.001	intracarotid	110
	Rabbit	0.5–15.0 μg	intracarotid	111, 112
	Rabbit	0.4–3.0 μg	intracarotid	113
Physostigmine	Cat	0.5–1.0	intraperitoneal	114
	Cat	0.25	intravenous	108
	Cat	0.025–0.1	intraperitoneal	115
	Rabbit	0.1	intravenous	116, 117 118, 119
	Rabbit	0.035–0.1	intracarotid	113
	Rabbit	0.15–0.25	intravenous	120
	Rabbit	0.1–0.3	intravenous	121, 122, 123 124, 125, 126
Nicotine	Cat	0.2–0.4	intravenous	106
	Rabbit	0.1	intravenous	127
	Rabbit	0.1	intravenous	128
	Rabbit	0.01–0.03	intravenous	129
Arecoline	Cat	0.3	intravenous	106
	Rabbit	0.1–0.4	intravenous	130
Pilocarpine	Rabbit	0.3	intravenous	113
Galanthamine	Cat	1.0–10.0	intravenous	106, 131
Isoflurophate (DFP)	Rabbit	0.05–0.3	intracarotid	111

not penetrate the blood-brain barrier and have therefore only a peripheral effect (51, 69). This quality makes it possible to use these drugs for the specific blockade of the peripheral cholinergic effect in the study of their central action. Using this method, Pfeiffer (49) has demonstrated the specific central effect of arecoline in animals as well as in patients. Lukomskaya (51) has established that arecoline and nicotine in small doses facilitate the formation of conditioned reflexes in mice, while anticholinergic drugs (caramiphen) retard the formation of conditioned reflexes under identical experimental conditions. Conversion into the methiodides of the cholinomimetic drugs, nicotine and arecoline, as well as the cholinolytic drug caramiphen, deprives these

drugs of any power to affect the rate of formation of conditioned reflexes, After a direct administration into the brain ventricle, the quaternary anticholinergic drugs proved to be very active even centrally (96). The lipid solubility is also very important for the central effect of these drugs (97, 98).

There is agreement in the literature that the anticholinergic drugs impair the acquisition of new impulses, whereas the well-learned responses are not influenced (52, 73). Herz (99) studied the effects of anticholinergic drugs on the complete cycle of conditioning and extinction in the rat. He used the "pole-climbing" technique and was able to demonstrate that atropine and scopolamine, when administered during the period of formation of the avoidance reflex, caused notable alterations in the response, while they were inactive in the fully trained animal.

Burešová et al. (64), using a simple one-atrial learning technique of the passive avoidance reaction in rats, showed that the exploratory behavior of naive animals was influenced neither by physostigmine nor by atropine. Neither drug influenced the consolidation process or the permanent memory. Learning and retention were, however, significantly affected. From these experiments they deduced that the system of cholinergic elements in the prosencephalon affected by physostigmine and atropine may play an important role in behavior functions such as acquisition of new experience and retrieval of threshold memory traces. Both drugs do probably cause a functional blockade of cholinoceptive synapses—either inactivation or overexcitation—with somewhat different side effects on related noncholinergic circuits.

Anticholinesterase drugs (neostigmine, physostigmine) in doses from 0.03 to 0.08 mg/kg will prevent the disturbance of the conditioned reflexes of dogs by cholinolytic drugs (atropine 0.17–0.5 mg/kg, caramiphen 1.0–10.0 mg/kg) (70). The antagonism in the action of cholinolytic and anticholinesterase drugs on the conditioned reflex activity supports the view that there are cholinergic synapses in the cerebral cortex. Particularly interesting is the fact that the central effects of anticholinergic compounds seemed to reach a maximum and then show virtually no change over large variations in dosage, sometimes even evoking the opposite effect (94, 100).

In the extensive papers published recently and dealing with the problem of the influence of cholinergic drugs on behavior (94, 101–103), the authors discussed the possible mechanism of their action on psychic function. One explanation is that these drugs cause a defect in recent memory (79, 81, 103). Other hypotheses suggest that the effects of anticholinergic drugs impair the biologically important mechanism suppressing all the stimuli not having biological significance [the extinction mechanism (101)].

Effect of Cholinomimetic and Anticholinergic Drugs on Electrical Activity of Brain in Experimental Animals

There has been a growing interest in the past years in the study of the effect of cholinergic drugs on the electrical activity of the brain, and several

reviews have summarized the recent knowledge, from different points of view (104–106).

Very soon after the discovery of the electrical activity of the brain, there were attempts to prove the importance of acetylcholine in brain function and to study the action of drugs on the supposed central cholinergic effect. It is natural that the first substance used for this purpose was acetylcholine. As acetylcholine does not easily penetrate the blood-brain barrier, the topical application to the exposed cerebral cortex of anesthetized animals has been used, the electrical activity being recorded either from the area to which the drug had been applied, or adjacent areas. Miller et al. (107) obtained spike discharges, and also motor effects, when they applied a 1 per cent solution of acetylcholine to an area of the exposed cortex previously treated with 1 per cent physostigmine.

Funderburg & Case (108) applied more concentrated solutions of acetylcholine in their study of the effect of atropine on cortical potentials. They also used drugs other than acetylcholine to produce the spiking in the EEG of anesthetized cats, e.g., penicillin, *d*-tubocurarine, and Intocostrin.

Another way to estimate the difficulty in the penetration of acetylcholine through the blood-brain barrier is to inject it intracisternally. After this administration, Forster (109) obtained depression of electrical activity, followed by high voltage discharges. Rather high doses, however, were used to evoke this effect (10 to 25 mg of acetylcholine). When acetylcholine was injected in sufficient dose into the blood circulation of the brain, i.e., into the carotid artery, the EEG arousal reaction was evoked (110–112). Action of acetylcholine injected into the carotid became effective with a dose of 0.5 μg; with larger doses of 1 μg to 5 μg the action was better developed and of longer duration.

Monnier & Romanowski (113) injected into the carotid artery not only acetylcholine, but also physostigmine and pilocarpine. They stated that the arousal syndrome was characterized by desynchronized electrical activities in the neocortex with synchronization in the hippocampus, caudate nucleus, thalamus, and midbrain reticular system. The arousal reaction to sensory and reticular stimuli was increased. Cortical potentials were also slightly increased by stimulation of the reticular system, and markedly increased by stimulation of the hippocampus and caudate nucleus. Recruiting potentials evoked by stimulation of the medial thalamus were increased, whereas cortical potentials evoked by stimulation of the ventrolateral thalamus were unaltered or slightly decreased. Most of these effects were suppressed by atropine. The authors stated that these facts prove the existence of cholinoceptive substrates inhibiting synchronization in the neocortex and of other cholinoceptive substrates facilitating synchronization in the archicortex (hippocampus) and caudate nucleus.

Physostigmine (eserine) is one of the drugs most used to evoke the cholinergic activation of the bioelectrical potentials in the brain and for the study

of the central effect of the anticholinergic drugs. It penetrates easily into the brain from the blood circulation, its peripheral effect in a suitable dose is low, and the central effect lasts several minutes, or longer, according to the dose used. Bradley & Elkes (114) used physostigmine for the evaluation of the central effect of *l*-hyoscyamine in the conscious unrestrained cat, using an implanted electrode technique (114, 115). Physostigmine alone produced fast low activity (of the "alert" type) without necessarily making the animal alert. In doses of 0.5 to 1 mg/kg, physostigmine abolished the slow activity produced by atropine and *l*-hyoscyamine. Simultaneous recordings of blood pressure and electrocortical activity in acute preparations have shown cortical activity to be unrelated to the transient changes in blood pressure produced by these drugs.

Benešová, Votava, and their co-workers used the physostigmine EEG arousal in rabbits with implanted cortical and subcortical electrodes (hippocampus, thalamus) for the evaluation of the central anticholinergic effect of imipramine-like drugs (116–119). They claimed that the "theta activity" in the hippocampus and the thalamus was especially suitable for the determination of the duration of the physostigmine effect. Physostigmine restored not only the EEG changes caused by scopolamine, but also the behavior impairment (120).

Extensive research on the EEG effect of cholinergic drugs has been done by White et al. (121–126). They studied the site of the activating effect of physostigmine and anticholinergic drugs in the brain of rabbits, using the transection method of brain stem in different levels. They stated that physostigmine produced an EEG activation in animals transected at the pontomesencephalic junction, but not in those transected in the midbrain. Transection at the posterior border of the pons resulted in an animal which manifested a persistent, alert EEG. This EEG pattern was changed to a synchronous one by the administration of atropine. They came to the same conclusion as Rinaldi & Himwich (111, 112, 137), that the alerting effect of cholinomimetics is localized in the midbrain reticular formation, which is of a cholinergic character. Physostigmine antagonized not only anticholinergic drugs, but also the synchronizing EEG effect of hypnotics and neuroleptics (122). Some of the phenothiazine derivatives, on the other hand, showed central anticholinergic action (promethazine, diethazine) (124).

Nicotine has been studied very intensively in the past years in EEG effects. It evokes a short-lasting arousal effect in the EEG, which is antagonized by relatively low doses of thymoleptic drugs (imipramine-like) (127, 128). A conference of the New York Academy of Sciences on the central effects of nicotine has recently been held and the material will soon be published in their Annals. Domino & Yamamoto presented interesting results on the "nicotinic" and "muscarinic" central receptor and on the ability of nicotine to evoke slow-wave sleep (129).

Herz (130) studied the central effect of arecoline on the EEG and behavior

and recommended a method using EEG arecoline arousal after elimination of the peripheral effect by methylatropine, for the study of the central "muscarinic" receptor.

Extensive research of the cholinergic structure in the reticular formation of the cat brain has been done by Ilyuchenok (131). He, too, stated that the cholinergic systems of the midbrain reticular formation no doubt play an important part in the EEG activation mechanism.

Effect of anticholinergic drugs on the electroencephalogram of the experimental animal has been studied by numerous scientists (see Table VII). All these drugs are qualitatively similar. They antagonize the EEG and the behavioral effects of central cholinomimetics (132–140). There are differences in the intensity of the effect. Most effective of these drugs is scopolamine, followed by *l*-hyoscyamine and benactyzine (123,133,143). The anticholinergic hallucinogenic drugs, e.g., Ditran (JB-329), have a strong effect on the EEG (115, 132). The antiparkinsonic drugs (trihexyphenidyl, etc.) also effectively influence the function of the mesodiencephalic activating system (137, 146).

There is now general agreement that the "dissociation" between the EEG synchronizing effect and the influence on the behavior, stated and described first by Wikler (140) in the dog, is only a relative one. However, very low doses of atropine-like drugs, which have substantial effect on the EEG, change the behavior considerably less than the drugs of other pharmacological groups. Denisenko (144, 145) summarized the results obtained by Soviet scientists in this field of research in these three points: (*a*) Cholino-reactive systems of certain formations of the brain are predominantly nicotine-sensitive or muscarine-sensitive. For example, in the reticular formation of the midbrain, the latter system prevails. (*b*) The part played by different cholino-reactive structures in the functional activity of the brain varies. The muscarine-sensitive systems of the cortex are probably involved in the transmission of predominantly inhibitory impulses. (*c*) Even among similar nicotine-sensitive and muscarine-sensitive systems of the brain there are differences in their individual reactions to stimulating and blocking agents. For example, the muscarine-sensitive systems of the reticular formation of the midbrain are blocked by benactyzine more easily than are those of the cortex.

It is evident that the conceptions of various scientists studying the central cholinergic system from the pharmacological and physiological point of view are in good agreement.

Concluding Remarks

The evidence of cholino-sensitive structures in the brain and of the important role of acetylcholine in central nervous activity is today many-sided. It was only possible to include a small part of it in this review. The establishment of the "hallucinogenic" effect of the central anticholinergic drugs has been particularly important. This is discussed in another review in this volume (147). Another important point is the treatment of certain psychoses by high doses of anticholinergic drugs (148–150). This therapy has now been used in

TABLE VII

EFFECT OF ANTICHOLINERGIC DRUGS ON THE ELECTROENCEPHALOGRAM OF THE EXPERIMENTAL ANIMALS

Drug	Animal	Dose mg/kg	Administration	References
Atropine	Cat	0.4–1.0	intravenous	108
	Cat	2.0–3.0	intraperitoneal	114
	Cat	0.5–2.5	intraperitoneal	115
	Cat	2.0	intraperitoneal	132
	Rabbit	0.5–1.0	intravenous	133
	Rabbit	0.001–5.0	intravenous	134
	Rabbit	0.2–0.4	intravenous	135, 136
	Rabbit	1.5	intravenous	113
	Rabbit	0.5–1.0	intravenous	112
	Rabbit	1.0–10.0	intravenous	137
	Rabbit	2.0–4.0	intravenous	123
	Rabbit	2.0	intravenous	126
	Rat	6.0	intraperitoneal	138
	Rat	3.0–12.0	intraperitoneal	139
	Dog	7.2	subcutaneous	140
	Rabbit	0.5–50.0	subcutaneous	141
	Dog	0.5–50.0	subcutaneous	141
	Monkey	1.5–60.0	intramuscular	141
Scopolamine	Rabbit	0.03–0.08	intravenous	136
	Rabbit	0.05–0.3	intravenous	120
	Rabbit	0.1–0.5	intravenous	123
	Dog	0.5–150.0	subcutaneous	141
	Monkey	1.5–60.0	intramuscular	141
	Rat	0.13–1.05	subcutaneous	142
l-Hyoscyamine	Rat	1.0–8.0	subcutaneous	142
	Dog	0.1-2.0	intravenous	143
Benactyzine	Rabbit	0.1–0.5	intravenous	133
	Rabbit	0.1–0.2	intravenous	123
	Rabbit	1.0	intravenous	144, 145
Ditran	Cat	1.0	intraperitoneal	132
	Cat	0.025–0.1	intraperitoneal	115
Imipramine	Rabbit	1.25–5.0	intravenous	117, 119
Trihexyphenidyl	Rabbit	1.0–10.0	intravenous	146

several psychiatric hospitals with good results and it offers an exceptional occasion for basic research on the effect of cholinergic drugs on the human psychic functions. The research in the field of the central cholinergic structure is therefore very important from both the theoretical as well as the practical point of view.

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