MECHANISMS OF AMIZYL (BENACTYZINE) AND DIPHACIL ACTION ON THE BRAIN

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ABSTRACT:

Proof is presented that amizyl and diphacil not only block the central choline receptors, but have an effect on the presynaptic reservoirs of mediators. Amizyl releases noradrenalin from the synaptic vesicles. Diphacil stabilizes the presynaptic reservoirs of catecholamines, nicotine releases noradrenalin and, apparently, dopamine from the presynaptic reservoirs. It is proposed that the basis of action of nicotine on the brain is release of catecholamines from their presynaptic reservoirs and that central n-cholinolytics prevent this action of nicotine.

The article is a correlated result of experimental work with amizyl and diphacil. hypothesis is introduced in it, on the mechanism of action of nicotine and the so-called central n-cholinolytics on the brain.

The first step in study of the central effects of amizyl and diphacil was an investigation of their effect on conditioned reflexes. It was established [4, 9, 10, A. T. Selivanova, 1969] that amizyl disrupts conditioned reflexes, in doses, at which unconditioned reflexes are unchanged. Diphacil disrupts conditioned and unconditioned reflexes to equal degrees.

It might be assumed that the m- and n-cholinolytics block the interactions of neurons with each other and, in this manner, suppression of the higher functions of the brain takes place. However, data have gradually been accumulated, which do not fit into this simple scheme. For example, it was noticed that amizyl reinforces the action of adrenalin [9], and also the central effects of phenamine [11]. Subsequent research showed that the noradrenalin content of the brain decreases, as a result of the action of amizyl, glipin [12, 15, 16, 20] and diphacil [36, 5]. In this case, the dopamine level, according to the data of V. M Demchenko and N. A. Vorob'yeva [5], does not change. Amizyl

directly frees noradrenalin from isolated synaptosomes and from isolated synaptic vesicles.

Atropine, scopolamine and other m-cholinolytics reduce the acetylcholine content of the brain [33, 37].

Amizyl suppresses MAO activity [41, 40, 19].

With daily use of amedine, amizyl, atropine and other cholinolytics, both in therapeutic practice [3, 27, 39] and under experimental conditions [7, 22, 38], reduction in the effect of these compounds on the central nervous system is observed (for example, if a state of stupefaction, similar to intoxication, arose in patients, in the first 3-5 days of use of cholinolytics, this effect of cholinolytics disappeared on subsequent days).

In tests on rats, with daily administration of amizyl, it was determined [13, 14] that, in the first 3-5 days, the noradrenalin content of the brain decreases sharply. The conditioned reflexes of all experimental animals were disrupted on these days. Beginning with the fifth day, the noradrenalin releasing effect of amizyl gradually decreases and, during the subsequent days. following routine administration of amizyl, the noradrenalin content of the brain scarcely differed from the initial level. In parallel with this, beginning on the ninth-tenth day, in practically all the animals, disruption of stable conditioned reflexes does not arise after routine administration of the cholinolytic. Moreover, the blockage of the m-choline receptors of the brain and slow, high-amplitude activity on the EEG appear each time, after routine daily administration of the cholinolytic, and it is retained in the same form as after the first (single) administration of amizyl [17]. During blockage of the central m-choline receptors, the ability of the brain to form

new conditioned reflexes is completely lost, both with a single and a prolonged daily administration of amizyl. This effect of amizyl coincides in time with the presence of slow, high-amplitude activity on the EEG [2].

All the data presented show that the central effects of amizyl are made up of two parallel processes: a) direct, releasing noradrenalin and the acetylcholine action of this cholinolytic in the corresponding presynaptic structures; b) blockage of the post-synaptic choline reactive structures (the so-called m-choline receptors) of the brain.

It can be stated that the direct release of noradrenalin and acetylcholine from the presynaptic structures (apparently of all sections of the brain), caused by amizyl, leads to disruption of the excitation and inhibition relationships built up between the neurons. As a result, disorganization of the brain function sets in. All of the conditioned reflex activity of the brain, including stable conditioned reflexes, are disrupted, because of this type of action of amizyl. It is curious to note that an adaptation develops very quickly to the noradrenalin released and the disrupted stable conditioned reflexes, due to the action of amizyl, with daily administration of the cholinolytic. The mechanism of this phenomenon still remains unknown.

As a result of blockade of the m-choline receptors of the brain, a slow, high-amplitude activity appears on the EEG [42, and others], and suppression of learning is noted (cutting off of remembering of current events). Based on this, it can be stated [1] that one of the significant functions of the acetylcholine mediator system of the brain, in particular, of its post-synaptic choline receptor apparatus, is formation of memory.

Moreover, N. R. Yelayev and colleagues [6] determined that, under specific conditions, considerable activation of RNA and protein synthesis takes place in the brain neurons, as a result of the action of amizyl. This correlates well with blockade of the central m-choline receptors. On the basis of these results, it could be proposed that, besides accomplishment of memory, a second very important function of the m-choline receptor apparatus (m-choline protein receptors) of the brain apparently is their participation in regulation of protein synthesis in the cells. If this point of view is competent, the choline receptor block, in this case, probably fulfills the role of cellular protein synthesis regulator, as a repressor.

For the purpose of analysis of the central effects of various cholinolytics, the effect of diphacil on the brain was studied, in parallel with the amizyl tests. Besides diphacil, another n-cholinolytic, tropazine, was studied in a portion of the tests. It was shown that the noradrenalin content of the brain, not only does not decrease, as a result of the action of diphacil and tropazine, but it even increases somewhat [12, 15, 16]. Diphacil has practically no effect on the acetylcholine content of rat brain.

During study of the effect of diphacil on the noradrenalin synaptic vesicles, it was found that diphacil somewhat increases the noradrenalin content in them. More than that, it was noticed in these tests that diphacil, as it were, locks noradrenalin into the vesicles and makes these vesicles inaccessible to release of the amine. On the basis of these data, it can be proposed that, on the one hand, the effect of diphacil on the brain consists of its locking of the presynaptic catecholamine reseroirs (dopamine and noradrenalin) and, not in blockage of hypothetical n-choline receptors of the brain; on the other

hand, simultaneous with locking of the presynaptic catecholamine reservoirs, diphacil can block the m-choline receptors of the brain [26, 27 and others].

In connection with these data on the mechanism of action of diphacil on the brain neurons, the hypothesis was formed that the central effects of nicotine (including the nicotine tremor) are caused, not by excitation of the n-choline receptors of the brain, but arise, as a result of release of noradrenalin [30, 31, 35] from the corresponding presynaptic reservoirs. The question of the significance of the acetylcholine releasing action of nicotine in this effect remains open. We began to study this possible effect of nicotine on the brain. The first experimental data turned out to be very encouraging. It was determined that nicotine decreases the noradrenalin level in the rat brain to approximately 56% of the initial level. Nicotine causes discharge of noradrenalin from isolated synaptosomes, also to approximately 50% of the initial amount. In tests with preliminary administration of diphacil or tropazine to rats, 15 min before administration of nicotine, it was found that the noradrenalin level in the brain decreased only to approximately 75% (diphacil) or 90% (tropazine) of the initial level, i.e., the catecholamine releasing effect of nicotine decreased significantly, as a result of the action of diphacil and tropazine.

These data permit a new description of the mechanism of the central effects of nicotine and the action of the so-called n-cholinolytics in the central nervous system.

Nicotine tremor apparently is the result of the release of noradrenalin from the corresponding presynaptic reservoirs, caused by nicotine. The absence of the effect, with repeated administration of nicotine in the next hours

which is considered in the literature to be a second, cholinolytic phase of action of nicotine: the so-called n-cholinolytic effect of nicotine [8, 25, 29, 27, and others]) is, thus, a result of generation of a noradrenalin deficiency (its level cannot be quickly restored), and not of a blockade of the n-choline receptors. In this situation, nicotine tremor can be prevented in two ways. One of them apparently consists of the noradrenalin reservoir locking effect of the corresponding compounds, the diphacil type so-called central n-cholinolytics. The second is caused by blockade of the adrenalin receptors by the corresponding adrenalin blockers. The possibility of the second pathway is confirmed by data that the nicotine tremor is suppressed (prevented) by adrenalin blockers [32, 21, 23, 24, 18].

From the situation of the effect of nicotine on the presynaptic catecholamine reservoirs and, apparently, acetylcholine, some antistressor and concentration and, to a certain extent, performance-raising capacity of smokers, the effect of smoking tobacco is more understandable. In all likelihood, this effect is caused by the fact that, with frequent smoking of cigarettes, the noradrenalin stores in the corresponding emotion-generating structures of the brain are decreased. In connection with this, excitation of these structures apparently is significantly decreased.

On the whole, from the point of view of our hypothesis on the mechanism of action of amizyl, diphacil and nicotine on the brain, it appears to be possible to more completely comprehend all the known factual data on the effects of these and similar compounds in experimental studies and in their therapeutic use.

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[Translator's note: Remainder of Bibliography not furnished.]