PRINCIPAL PHARMACOLOGICAL PROPERTIES OF SOME 2-SUBSTITUTED TRYPTAMINES

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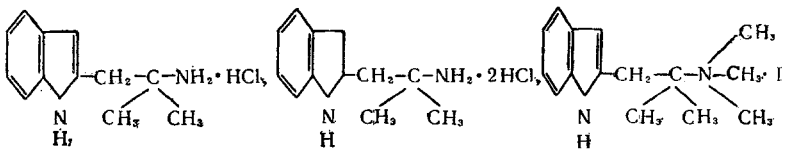
The part played by tryptamine in the execution of the functions of the central nervous system is a problem currently engaging the attention of researchers [4, 7, 9, 10].

In this connection it is interesting to study the relationship between the chemical structure and the pharmacological action of tryptamine. One attempt made in this direction was the investigation of the subtituted tryptamines synthesized by N. F. Kucherova and N. N. Komzolova, in which the side chain is in position 2 relative to the nitrogen, unlike in the previously studied indole derivatives—tryptamine, serotonin, etc., which are subtituted in position 3.

This communication describes some of the pharmacological properties of the following compounds: NK-122 [2-(2-methyl-2-amino)-propylindole hydrochloride], NK-95 [2-(2-methyl-2-amino)-propylindoline dihydrochloride], and NK-146 [2-(β-dimethylaminoisobutyl)-indole methiodide]:



NK-122 NK-95 NK-146

EXPERIMENTAL RESULTS AND DISCUSSION

Administration of NK-122 (10-30 mg/kg, intravenously) and NK-95 (5-20 mg/kg) to mice and rats caused characteristic changes in behavior (generalized motor excitation, tremor of the limbs and tail, stereotyped spasms of the head). This action was intensified by the preliminary administration of iproniazid [3].

NK-122 and NK-95 acted antagonistically on the depression of motor activity and ptosis caused in mice by reserpine (2 mg/kg intraperitoneally). The effective dose in this respect, calculated by Vane's method [11], was 20 mg/kg for NK-95 and 36 mg/kg (intraperitoneally) for NK-122. The quaternary compound NK-146 did not give the effects described above.

Chronic experiments performed on unanesthetized, uncurarized rabbits with implanted electrodes showed that NK-122 (starting with a dose of 5-6 mg/kg, intravenously) and NK-95 (with a dose of 2-3 mg/kg) caused fast waves (up to 20-25 cps) of low amplitude (up to 25-30 μV) to appear in the sensorimotor areas of the cortex. In these circumstances, a regular rhythm of 4-6 cps, 40-50 μV, was recorded in the association and optic areas of the cortex, the reticular formation of the mesencephalon, the antero-ventral nucleus of the thalamus, and the hippocampus (Fig. 1). The changes described above, characteristic of the EEG activation reaction, developed immediately after administration of the compounds and lasted for between 30-40 min and 1-2 h. These changes in the EEG were accompanied, especially if the dose was increased to 10-20 mg/kg, by changes in behavior (timidity, tremor of the head), and the rabbits developed an increased respiration rate, exophthalmos, and bradycardia.

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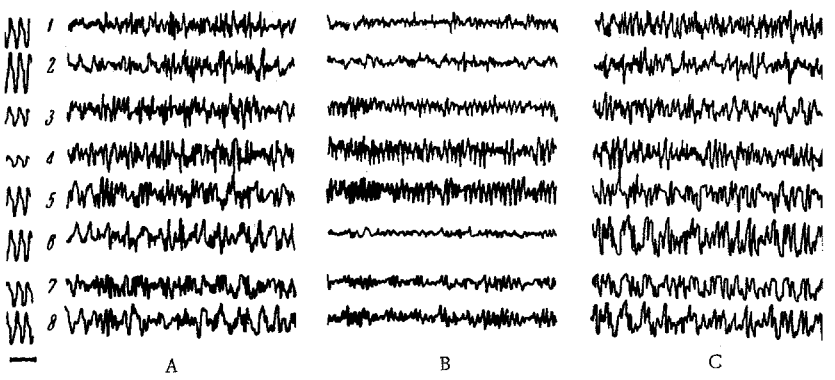

Fig. 1. Effect of NK-95 on the EEG of a rabbit. 1) anterior; 2) posterior sensorimotor area of the cortex; 3) antero-ventral nucleus of the thalamus; 4) mesencephalic reticular formation; 5) hippocampus; 6) association area; 7 and 8) optic area of the cortex. A) before injection; b) 10 min, and c) 3 h after injection of NK-95 in a dose of 5 mg/kg intravenously. Calibration 100 μV, 1 sec.

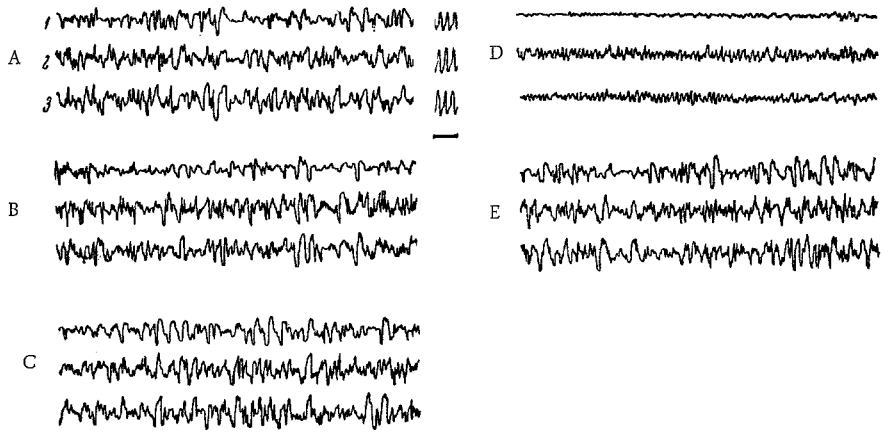

Fig. 2. Effects of tertiary and quaternary tryptamine derivatives when injected intravenously. 1) anterior sensorimotor; 2) optic; 3) association areas of the rabbits's cerebral cortex. A) before injection; B) 45 sec after injection of NK-146 in a dose of 2 mg/kg; C) 2 min after injection of NK-146 in a dose of 5 mg/kg; D) 2 min and E) 2 h after injection of NK-122 in a dose of 5 mg/kg. Calibration 100 μV, 1 sec.

Having obtained results indicating that identical receptors are excited by serotonin and tryptamine [10], the next step was to study the action of certain serotonin antagonists on the electroencephalographic effects of the test compounds. Using the same animals (at intervals of 7-10 days) a comparison was made of the dose of compounds NK-122 and NK-95 causing activation of the EEG in the absence of premedication with their doses causing activation against the background, either of morphine in a dose of 3-5 mg/kg (blocking the M receptors) or of dihydroergotoxin and dihydroergotamine in a dose of 5-6 mg/kg (blocking the D receptors) [6]. Administration of the ergot alkaloids did not significantly change the activating dose of the tryptamine derivatives established for a particular animal. Morphine had an obviously antagonistic effect on the EEG changes caused by the tryptamine derivatives: against its background 4 or 5 times larger doses of these compounds had to be given to produce activation than in the controls, and in some animals no activation could be obtained even with these doses. However, the subsequent administration of amphetamine caused activation, demonstrating that the blocking action of morphine possesses some degree of specificity. This is confirmed by another fact: if a slow, low-amplitude EEG characteristic of the action of tranquilizers was produced not by morphine, but by Nembutal (6 mg/kg, intravenously), administration

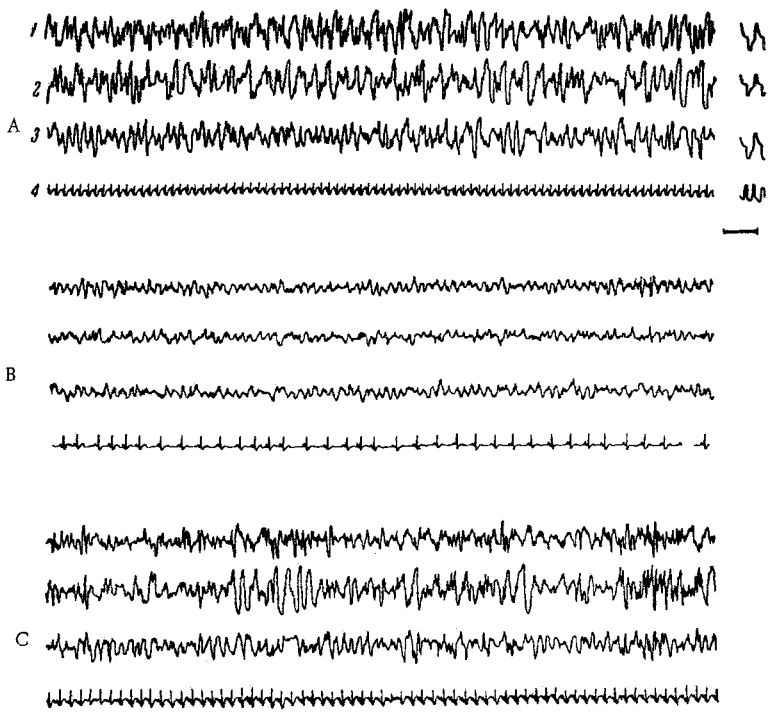

Fig. 3. Activating effect of NK-146 when injected into the lateral ventricle. 1-3) EEG (legend as in Fig. 2); 4) ECG. A) before injection; B) 35 min and C) 3.5 h after injection of NK-146 in a dose of 0.05 mg.

of usually activating doses of the tryptamine derivatives led to distinct activation. In the study of the activation produced by the precursor of serotonin—5-hydroxytryptophan—the same phenomenon was observed: it was blocked by morphine but not by the dihydrogenated ergot alkaloids. It may accordingly be concluded that structures of the M type are concerned in the mechanism of the activating effect of the precursor of serotonin and of the tryptamine derivatives. It was technically impossible to investigate the role of the receptors of T type (Pidevich's nomenclature) in the mechanism of the reaction, because the substance blocking the T receptors (tipindole), as we have shown, itself produces the EEG activation reaction.

The compound NK-146, when injected intravenously in doses of 1-10 mg/kg, did not evoke EEG activation (Fig. 2), unlike its tertiary analog. However, when injected into the lateral ventricle, in a dose of only 0.05 mg, a distinct activation reaction was observed (Fig. 3), lasting for 2-3 h. It was accompanied by a tremor, an increased respiration rate, and bradycardia.

Experiments on the isolated rat's stomach [11] showed that all three compounds have a serotonin-like action: in concentrations of 10^{-8}–10^{-7} they cause contraction of a strip of stomach, just as is observed by the action of serotonin in a concentration of 10^{-9}.

The value of LD_{50} (by the method of Litchfield and Wilcoxon; experiments on albino mice) was: for NK-146, 10.3 (8.9-11.9) mg/kg, for NK-95, 89 (77.39-102.35) mg/kg, and for NK-122, 120 (106.2-135.6) mg/kg when injected intravenously.

NK-95 and NK-122 thus had a clear effect on the central nervous system, as demonstrated primarily by their ability to produced tremor, stereotyped movements, and other disturbances of motor activity analogous to those described for tryptamine [10] and its alkyl derivatives [12]. The effect of both disubstitued compounds—NK-95 and NK-122—on the EEG was similar to the effect of tryptamine and its derivatives [5, 8]. The slight differences in the degree of the reaction of EEG activation reported by different authors were evidently attributable to technical factors, including the use of different animals [2], and also with the acute or chronic character of the experiment. It seems likely that the activation from the tryptamine derivatives in the acute experiment is less marked as a result of the application of procaine ot the wound surfaces, carried out in these conditions. The resorptive action of the procaine, which possesses antiserotonin activity, cannot be excluded in these circumstances.

A comparison with data in the literature indicates that displacement of the side chain into position 2 causes no essential change in the character of the action of tryptamine derivatives. Comparison of the activity of the compounds themselves showed that hydrogenation in position 2-3 of the pyrrole ring (NK-95) causes a small increase in activity (by comparison with NK-122). It follows from the preliminary study of compound K-272 [2-(2-methyl-2-methylamino)-propylindole hydrochloride] that the replacement of one hydrogen atom of the amino group in the side chain by a methyl radical weakens the central action. The conversion of the tertiary nitrogen atom of the side chain into quaternary (compound NK-146) causes loss of the central action (absence of tremor and EEG activation on intravenous injection) and an increase in the peripheral effects (bradycardia, pressor effect, high toxicity). Although no reports could be found in the literature of the investigation of compounds of this series, the change in the action described afer quaternization may be explained from the standpoint of the general principle that the presence of a quaternary nitrogen atom in a molecule makes it more difficult for the molecule to pass through the blood-brain barrier.

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