COMPARISON OF THE T-ANTISEROTONIN ACTIVITY OF SOME INDOLE AND BENZOFURAN DERIVATIVES

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UDC 615.212.7 : [547.751 + 547.722].015.4 : 612.015.3 : 547.757

Experiments on anesthetized cats showed that benzofuran derivatives ALA-455 and K-320 are much less active than the corresponding derivatives of indole (ALA-251 and NSH-134) in their ability to depress reflex bradycardia in response to serotonin (T-antiserotonin activity). The results are discussed from the point of view of the possible role of indole nitrogen in the interaction between serotonin antagonists and T-serotoninergic structures.

The writer's previous investigations showed that the Bezold–Jarisch reflex to serotonin arises from serotoninergic structures which differ significantly from those described previously in their resistance to lysergic acid derivatives and to the narcotic analygesics. These structures are competitively blocked by tipindole (the β-dimethylamino-ethyl ester of 1,3,4,5-tetrahydrothiopyrano-(4,3-B)-indolecarboxylic-8 acid), and for this reason they have been described as T-serotoninergic [4-5]. Further investigations showed that, like tipindole, other derivatives of indole also possess T-antiserotonin properties, notably the substances ALA-251 and NSH-134 (the dimethylaminoethyl esters of 2,3-dimethylindolecarboxylic-5 acid and 3-methyl-1,2,3,4-tetrahydro-γ-carbolinecarboxylic-6 acid) [6]. The object of the present investigation was to compare the T-antiserotonin activity of compounds ALA-251 and NSH-134 with the corresponding activity of their oxygen isosteres – derivatives of benzofuran synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR, by L. A. Aksanova and co-workers.* This comparison would be interesting to clarify the role of indole nitrogen in the manifestation of the T-antiserotonin activity of these compounds.

EXPERIMENTAL METHOD

Altogether 50 experiments were performed on cats anesthetized with urethane (600 mg/kg) and chloralose (40 mg/kg). Serotonin and its antagonists were injected intravenously. The arterial pressure was recorded in the carotid artery by a mercury manometer. The heart rate was determined from the blood pressure curve. The T-antiserotonin activity of the compounds was estimated from their ability to double the threshold of reflex bradycardia to serotonin.†

*The oxygen isostere of tipindole was also synthesized. However, this compound was found to be very rapidly hydrolyzed in solutions, making quantitative estimation of its activity difficult.

†The Bezold–Jarisch reflex to serotonin is manifested by bradycardia, hypotension, and apnea. The cardiac component of this triad was chosen because it is purely reflex in character in cats, whereas the hypotension and, in some cases, the apnea are mixed [5].

Laboratory of Pharmacology of the Cardiovascular System and Laboratory No. 1 of Organic Synthesis, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR, V. V. Zakusov.) Translated from Byulletin' Éksperimental'noi Biologii i Meditsiny, Vol. 72, No. 11, pp. 52-54, November, 1971. Original article submitted November 26, 1970.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that indole derivatives are much stronger than the corresponding oxygen isosteres in their T-antiserotonin activity. For instance, compound ALA-251 doubled the threshold of reflex bradycardia to serotonin in a dose (M ± m) of 0.38 ± 0.01 mg/kg, while the corresponding benzofuran derivative, compound ALA-455, produced this effect only in a dose of 2.42 ± 0.027 mg/kg. In both cases the antagonism was specific, for reflex bradycardia to sodium salicylate was not reduced by these compounds even in a dose of 5 mg/kg. The indole derivative NSH-134 doubled the threshold of reflex bradycardia to serotonin in a dose 0.64 mg/kg, while the corresponding oxygen isostereldid not depress this reflex in a dose of 5 mg/kg. The presence of the indole nitrogen thus is an important condition for T-antiserotonin activity of the tested compounds.

Some properties distinguishing indole derivatives from benzofuran derivatives can be deduced from the comparison of the following characteristics of indole and benzofuran: indole has a higher net positive charge on the heterocyclic atom (+0.305 for indole nitrogen and +0.126 for the benzofuran oxygen), a higher negative charge on the C_3 atom (−0.111 for indole and −0.033 for benzofuran),* and a slightly higher electron density on the C_5, C_7, and C_8 atoms [13]. The net dipole moment of the indole molecule determined experimentally is 2.13 D, compared with 0.79 D for benzofuran [10]. Meanwhile, the interatomic distances in the indole and benzofuran rings are virtually identical.

The foregoing facts suggest that the greater T-antiserotonin activity of indole derivatives than of benzofuran derivatives can be explained by the better conditions for electrostatic interaction between particular fragments of the indole ring and the corresponding areas of the T-receptor. In this connection the further study of the dependence of the T-antiserotonin properties of substances on the net charges on the nitrogen and carbon atoms of the indole ring is interesting.

Besides the characteristics already mentioned, indole and pyrrole differ from their oxygen isosteres by their rather stronger electron-donor properties: the first ionization potential† of pyrrole, for instance, is 8.97-8.2, while that of furan is 9.03-8.89 [13]. This may account for the less marked tendency of the oxygen isosteres to form complexes with transfer of the charge. Nevertheless, the formation of complexes with charge transfer is regarded as a hypothetical means by which serotonin and its antagonists react with serotoninergic structures [2, 7, 11].

One of the distinguishing features of indole derivatives is evidently the presence of a hydrogen atom attached to the indole nitrogen, so that hydrogen bonding can take place between the indole nitrogen and any electronegative atom of the receptor. Benzofuran derivatives cannot act as donors for such a band. However, as this writer's investigation [1] showed, the ability of indoles to act as donors in hydrogen bonding is unlikely to play an essential role in the interaction of the antagonists with T-serotoninergic structures, because replacement of the hydrogen atom at the indole nitrogen by a methyl radical not only does not reduce but, on the contrary, it increases T-antiserotonin activity.

Further investigations will show which of the factors mentioned above, or which other factors which have not been considered, play the essential role in the interaction between these compounds and T-serotoninergic structures. However, it is already clear that the nitrogen of the indole ring is important for their T-antiserotonin activity.

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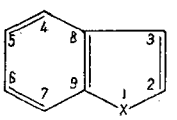
*The atoms of indole and benzofuran are numbered as follows:



†The first ionization potential of the π-electron is the energy required to remove one π-electron from the molecule in the gaseous phase. The higher the ionization potential, the less strong the electron-donor properties of the substance.

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