

EFFECT OF AN ANTAGONIST OF SEROTONIN ON PRESSOR RESPONSE OF VARIOUS COMPOUNDS¹

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Recently Wooley and Shaw (1952) have reported 2 active antagonists of serotonin, 2-methyl-3-ethyl-5-nitroindole and 2-methyl-3-ethyl-5-aminoindole. Since serotonin, 5-hydroxytryptamine, is a naturally occurring compound having vasoconstrictor activity, an investigation of the effect of a serotonin antagonist on various other vasoactive compounds of known and unknown structure seemed worthwhile. The object of this investigation was to test the specificity of the antagonist and possibly to elucidate active "vasoconstrictor groups" in the compounds of unknown structure.

Experimental. The antagonist used exclusively in this study was 2-methyl-3-ethyl-5-nitroindole* which has been reported to be active on oral administration (Wooley and Shaw, 1953). Male albino rats of the Wistar strain, weighing between 350 and 400 g were used. Two types of experiments were performed: (1) Normal rats were fed 50 mg of the compound *per diem* mixed in their ration for 5 days; (2) The compound, dissolved in propylene glycol, was administered to the anesthetized normal rats by intravenous injection (300 micrograms per 100 g body weight). For assay of pressor activity the animals were anesthetized with dial-urethane*, 0.08 ml per 100 g body weight intraperitoneally. A carotid artery was cannulated and connected to a direct reading mercury manometer for measurement of mean arterial blood pressure. All test substances were injected in a volume of 0.1 ml into the jugular vein. The following vasoactive materials were assayed: Phenethylamine 25, tyramine 20, L-arterenol 0.1, isoamylamine 150, tryptamine 20, serotonin* 5, histamine 2 micrograms respectively, and hypertensin, renin, pitressin and pepsitensin in amounts to produce an elevation in mean pressure of 20-30 mm Hg. These materials in the above concentrations were tested in control and antagonist-fed animals, and also before and after the administration of the antagonist by the intravenous route. In the latter case each animal served as its own control. The number of assays varied from 6 to 26 for each compound and each condition.

Results. The oral administration of 2-methyl-3-ethyl-5-nitroindole exhibited no toxic effects. In addition, there was no change in the mean systolic blood pressure, taken daily by the foot-cuff method of Kersten et. al. (1947), during the entire feeding period. Comparing the response to the vasoactive compounds

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studied, there was no difference between control and test-fed animals except for serotonin and tryptamine. In the case of these two compounds (Table 1) a reversal of the response was seen in the animals fed the antagonist; in other words, intravenous injection of serotonin or tryptamine produced a depressor instead of a pressor response.

TABLE 1

Mean blood pressure responses following injection of test compounds in control animals and animals given the serotonin antagonist.

| | CONTROL | AFTER SEROTONIN ANTAGONIST | |
|------------|--------------------|----------------------------|--------------------|
| | (No antagonist) | Orally | Intravenously |
| Tryptamine | +30.6± 9.9 (17) | -30.7±12.5 (8) | +23.2± 5.4 (6) |
| Serotonin | +35.5±13.8 (21) | -56.6±15.2 (12) | -38.1±13.5 (10) |

Values following means are the S. D.; the number of determinations are given in parenthesis.

On administration of the antagonist by very slow intravenous injection a temporary depression of the mean blood pressure was noted. This was not due to the solvent, propylene glycol, as this compound has no effect on blood pressure when injected alone. With the exception of serotonin, none of the substances studied showed a difference in response prior to and following the administration of the 2-methyl-3-ethyl-5-nitroindole. In every experiment the type and degree of vasoactivity was similar before and after treatment with the antagonist. The predominant action of serotonin *per se* was pressor, and after the intravenous administration of the antagonist it became depressor. These data confirm earlier reports on the complex nature of the serotonin response (Freyburger, et al., 1952, and Page and McCubbin, 1953).

The substituted nitroindole used in these studies was active orally probably due to its conversion in the body to the amino analog. After intravenous injection of the nitroindole, the action of serotonin was depressor while tryptamine still elicited a pressor response. This difference may be due to the possibility that the reversal of tryptamine action necessitated either a relatively larger amount of the amino analog or a further degradation product produced by enzymatic action in the intestine.

Since tryptamine is known to have an effect on the heart and serotonin an effect on pulmonary circulation, experiments

based on the overall vasoconstrictor action of these compounds are difficult to analyze. Despite the advisability of using the intact animal, isolated organs, such as arterial rings (Wooley and Shaw, 1953a), would be expected to give more interpretable results, at least until the mechanisms of action of serotonin and tryptamine have been elucidated.

Summary. The specificity of the antagonist of serotonin, 2-methyl-3-ethyl-5-nitroindole, has been studied and found to reverse the activity of serotonin and also tryptamine. This material is effective orally and in lesser degree intravenously. It does not change the basal systolic blood pressure, and has no influence on the activity of L-arterenol, tyramine, phenethylamine, isoamylamine, histamine, hypertensin, renin, pitressin, or pepsitensin. Since the antagonist did not influence the activity of these materials, these compounds of known and unknown structure may be presumed to have no vasoconstrictor groups similar to serotonin.

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