STRUCTURE-ACTIVITY RELATIONSHIPS OF SEROTONIN RECEPTORS IN ISOLATED SMOOTH MUSCLE

by

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TABLE OF CONTENTS

SUMMARY

The effects of substitution at the indole nitrogen of tryptamine on its smooth muscle contracting ability have been examined. Using serotonin (5-hydroxytryptamine) as a reference standard, tryptamine and its 1-methyl and benzo[b]thiophene isosteres have been tested as agonists on the isolated rat aorta and stomach fundus. The isosteres, as well as tryptamine, exhibited the same intrinsic activity as serotonin in both tissues. Analysis of the log dose-response curves showed that on aorta the test compounds acted via the same mechanism as serotonin and have similar affinities for the receptors. On stomach fundus serotonin had a much higher affinity for the receptors than did the other compounds. Tryptamine did not appear to act by the same mechanism as the other three agonists on stomach fundus.

Methysergide was used as a specific antagonist of serotonin in order to more fully elucidate the receptor mechanisms of the three compounds. On the aorta, methysergide did not act competitively against any of the compounds tested. However, the test agonists all interacted with methysergide in the same way, which suggests that they may act by the same mechanism as serotonin. On the stomach fundus, methysergide acted competitively against serotonin but not against the three test compounds, indicating that tryptamine and its isosteres do not act solely via serotonin receptors in the stomach. These three drugs interacted in the same fashion with methysergide, implying a common mechanism for tryptamine and its isosteres.

The author has concluded that serotonin receptors in the aorta and stomach fundus are different. Further avenues of investigation in order to define more fully the differences in the two tissues and to determine the mechanism of action of the test drugs have been suggested.