Mutagenicity of Azathioprine

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SUMMARY

Azathioprine (6-[(1-methyl-4-nitroimidazol-5-yl)thio]purine; Imuran) is mutagenic for Salmonella typhimurium. Demonstration of this mutagenic effect requires a period of anaerobic incubation of the bacteria with the test agent.

RESULTS

Azathioprine was without significant mutagenic potential (Table 1, Experiment 1) when exposure of the bacteria to the drug was carried out under the standard procedure developed by Ames et al. (1, 3). However, when the initial exposure of the bacteria to the test agent was allowed to occur under anaerobic conditions, a mutagenic effect was clearly demonstrable (Table 1, Experiment 1). This effect was dependent on azathioprine concentration (Table 1, Experiment 2).

DISCUSSION

Recent studies in this laboratory have indicated that the mutagenic potential of nitroheterocyclic substances could be greatly enhanced when the initial incubation was carried out under anaerobic conditions (unpublished results). This observation may reflect the oxygen-labile nature of the postulated hydroxylamino intermediate that is believed to represent an active metabolite (4, 6). Because azathioprine contains a nitro function, and in view of its lack of significant mutagenic activity when tested by the standard (aerobic) procedure, the assay was carried out under anaerobic conditions with a resultant demonstration of mutagenic activity.

Azathioprine is hydrolyzed in vivo and, under certain conditions in vitro, to 1-methyl-4-nitro-5-thioimidazole, 6-mercaptopurine, and other derivatives (5). It remains to be elucidated whether the mutagenic activity is due to azathioprine per se or to one of its metabolites.

The relevance of the present observation to a possible carcinogenic effect in humans remains to be established. The fact that an unusually high proportion of patients receiving azathioprine develop neoplasias suggests a possible relationship.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Bruce N. Ames, University of California at Berkeley, for providing them with the Salmonella strain used in this study.
Table 1

Mutagenic activity for S. typhimurium TA100

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<th>Experiment</th>
<th>Additions</th>
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<th>Revertants/plate</th>
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REFERENCES

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