Short report

Methyl groups or additional aromatic groups donate tumour promoting activity

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There are many examples in chemical carcinogenesis in which the introduction of methyl groups or aromatic rings increased the potency of polycyclic hydrocarbons and aromatic amines. Examination of the data in the light of the multistage process of carcinogenesis indicates that these groups convert initiators into complete carcinogens. As complete carcinogens have both initiating and promoting action, the added groups may be considered to have donated tumour promoting activity to the molecule. Such groups were once called “auxocarcinogens.”

Aromatic hydrocarbons

In none of many experiments with phenanthrene did it alone produce tumours but when it was applied to the skin of mice before treatment with croton oil or TPA the incidence of papillomas increased. Phenanthrene is therefore a tumour initiator. Two methyl derivatives 1,2,4-trimethylphenanthrene and 1,2,3,4-tetramethylphenanthrene were found to be weak but positive skin carcinogens.

Chrysene is a doubtful carcinogen. In an experiment a solution of 0.3% chrysene of “doubtful purity” was applied repeatedly to the skin of 50 mice producing two papillomas. These tumours could have been caused by other compounds in the material used. In many experiments pure chrysene was not carcinogenic. On the other hand, 5-methylchrysene is a potent skin carcinogen in mice.

Benz(a)anthracene is a weak or “disputed” carcinogen but is mutagenic in many systems—for instance Salmonella typhimurium. It also acts as an initiator when its application is followed by treatment with croton oil. In this series the effect of addition of groups is most striking. The 7 and 12 monomethyl derivatives are definite carcinogens and 7,12-di-methylbenz(a)anthracene is the most rapidly acting carcinogen—that is, the most potent tumour promotor of the complete carcinogens.

Benzene rings can have similar effects to methyl groups. Benzo(ghi)perylene is a moderately active complete carcinogen and derivative of phenanthrene. Benzo(a)pyrene can be considered as a derivative of either chrysene or benz(a)anthracene.

Conclusion

Clearly in many cases the increase in carcinogenic activity that occurs on introduction of methyl groups into the molecule is due to increase in the tumour promoting rather than initiating activity. The biochemical basis for this effect is not clear. 7,12-Dimethylbenz(a)anthracene is metabolised to 7-hydroxymethyl-12-methylbenz(a)anthracene but
**Initiators**

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**Complete carcinogens**

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Effect of methyl groups on carcinogenic activity.

This hydroxymethyl derivative is a slower carcinogen than the parent hydrocarbon.17

**References**

5 Delcos KB, Tapley WG, Miller EC, Miller JA. 4-Aminoazobenzene and N-N-dimethyl-4-aminoazobenzene as equipotent hepatic carcinogens in male SC7 BL/6 X C3H/HEF,mice and characterization of N-(desoxyguanosin-8-yl)-4-aminoazobenzene as the major persistent hepatic DNA-bound dye in these mice. *Cancer Res* 1984;44:2540–50.
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