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."¹

Aromatic amines

The demonstrations of the abilities of 0-aminoazotoluene² and 4-dimethylaminoazobenzene, butter yellow,³ to induce liver tumour in rats have been frequently repeated. In one experiment the compound without methyl groups, 4-aminoazobenzene, also induced liver tumours in rats fed a low protein diet in which potatoes were the main constituent.⁴ In their experiment the first tumour was seen after 525 days. The carcinogenic action of aminoazobenzene was not seen again until it was shown that it was carcinogenic in young mice.⁵ 4-Aminoazobenzene was considered to be a tumour initiator. The rapid growth of the young animals provides the stimulus that can be provided by known tumour promoters. These experiments show that the addition of methyl groups, either to the amino group or certain positions of the aromatic ring, convert an initiator into complete carcinogens (figure). The methyl groups have therefore donated tumour promoting activity to the molecule. It is remarkable that methyl groups are specifically active; 4-diethylaminoazobenzene is not carcinogenic.

As 4-aminoazobenzene induced tumours in rats when the main constituent of the diet was boiled potatoes, it seems possible that the potato diet had some tumour promoting activity.

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 oil⁶ or TPA⁷ the incidence of papillomas increased. Phenanthrene is therefore a tumour initiator. Two methyl derivatives 1,2,4-trimethylphenanthrene⁸ and 1,2,3,4-tetramethylphenanthrene⁹ 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.¹⁰ These tumours could have been caused by other compounds in the material used. In many experiments pure chrysene was not carcinogenic.¹¹ On the other hand, 5-methylchrysene is a potent skin carcinogen in mice.¹²

Benz(a)anthracene is a weak or "disputed" carcinogen but is mutagenic in many systems—for instance *Salmonella typhimurium*.¹³ It also acts as an initiator when its application is followed by treatment with croton oil.¹⁴ In this series the effect of addition of groups is most striking. The 7 and 12 monomethyl derivatives are definite carcinogens and 7,12-dimethylbenz(a)anthracene is the most rapidly acting carcinogen¹⁵—that is, the most potent tumour promotor of the complete carcinogens.

Benzene rings can have similar effects to methyl groups. Benzphenanthrene 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)anthracene¹⁶ but

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Initiators Complete carcinogens

Effect of methyl groups on carcinogenic activity.

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

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