The Effect of Folic Acid on A-Methopterin-induced Inhibition of Nucleic Acid Synthesis

HOWARD E. SKIPPER, CONSTANCE NOLAN, MARGARET ANN NEWTON, AND LINDA SIMPSON

(Biochemistry Division, Southern Research Institute, Birmingham, Ala.)

It has been observed that folic acid (2) or citrovorum factor (1) will prevent the anti-leukemic action of folic acid antagonists. We have reported that desoxyribonucleic acid (5) and vitamin B₁₂ (7) will partially prevent the anti-leukemic action of 4-aminopteroylglutamic acids, and have more recently observed that a combination of thymidine, adenylc, guanylic, and cytidylic acids or DNA plus RNA plus B₁₂ are more effective in preventing the anti-leukemic action of 4-amino-N₁⁰-methylpteroylglutamic acid (A-methopterin) than any of these materials administered alone.¹

mice treated with A-methopterin and with folic acid plus A-methopterin (in immediate succession) were injected with C¹⁴-formate (1.0 μC.), and at 6 hours the viscera were excised, pooled, and the combined nucleic acids and then nucleic acid purines were isolated (8) and assayed for radioactivity (6). The dosage schedules and experimental results obtained are summarized in Table 1.

**DISCUSSION**

It seems quite evident from the data presented that folic acid at high levels (60 mg/kg) will para-

| TABLE 1 | THE EFFECT OF FOLIC ACID ON A-METHOPTERIN-INDUCED INHIBITION OF NUCLEIC ACID SYNTHESIS |
|---|---|---|
| Exp. No. | Treatment | Dosage (mg/kg) | Specific Activities (μC/mmol Carbon) |
| | | | Visceral homogenate | Combined nucleic acids | Nucleic acid purines |
| 1 | None | | 4.5 | 18.9 | 75.6 |
| 2 | A-methopterin | 3 (×2) | 4.7 | 5.2 | 14.4 |
| 3 | A-methopterin | 2 (×2) | 4.8 | 6.8 | 19.4 |
| 4 | A-methopterin | 1 (×2) | 4.0 | 5.4 | 14.3 |
| 5 | A-methopterin+folic acid | 1+60 (×2) | 4.6 | 10.3 | 37.2 |
| 6 | A-methopterin+folic acid | 1+60 (×2) | 15.4 | 59.0 |

Note: Four mice were used in each experiment. About 1.0 μC. of formate was injected per mouse. The A-methopterin was administered intraperitoneally on the 8 days immediately prior to injection of C¹⁴-formate. Folic acid was injected I.P., as indicated, immediately prior to the injections of A-methopterin.

It is known that folic acid antagonists will inhibit incorporation of formate into visceral nucleic acids of mice and rats (8, 8). In view of the fact that the anti-cancer activity of A-methopterin appears to be directed toward inhibition of nucleic acid synthesis, it was considered of interest to determine whether this inhibition could be prevented by folic acid.

**EXPERIMENTAL**

Experimental procedures employed herein have already been described in detail (8). Adult CFW

¹ H. E. Skipper, M. Bell, and J. B. Chapman, unpublished data.

Received for publication December 24, 1951.
SUMMARY

Using C14-formate incorporation as a means of measuring the rate of synthesis of nucleic acids, it has been demonstrated that the inhibition of nucleic acid synthesis induced by A-methopterin can be partially reversed by folic acid.

REFERENCES

The Effect of Folic Acid on A-Methopterin-induced Inhibition of Nucleic Acid Synthesis

Howard E. Skipper, Constance Nolan, Margaret Ann Newton, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/12/5/369

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.