

FACILITATION BY POLYSORBATE 80 OF METHOTREXATE UPTAKE INTO MOUSE BRAIN

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Under some conditions we have found that polysorbate 80 enhances the absorption of moderately high dose methotrexate (MTX) from the mouse gastro-intestinal tract (Azmin and others 1982). Our results suggested also that nonionic surfactants might also promote transport of MTX into the brain. The aim of the present work was to confirm this possibility and also to determine whether increased transport into the brain, if any, was the result of increased plasma levels of the drug or to a more specific effect of the surfactant in reducing blood-brain barrier permeability.

Little is known about the absorption and distribution of nonionic surfactants in spite of their widespread use in pharmacy. In order to judge whether or not it was possible for polysorbate 80 to influence blood brain barrier permeability, the absorption of I¹²⁵-labelled polysorbate 80 was studied using gamma scintigraphy. In the rat between 10-50% of radiolabelled surfactant was found to be readily absorbed from the alimentary tract in 2 hours.

Intravenous administration of MTX-polysorbate solutions avoids the complication of changes in the bioavailability from the GI tract in the presence of surfactant. Groups of mice were injected with MTX solutions through the tail vein. 6 animals in each group were killed at intervals, the animals dissected and the blood, brain and other tissues of interest collected. MTX concentrations in the blood and tissues were determined using H.P.L.C. method. Results in Table 1 indicate that higher brain levels of MTX were achieved in mice given MTX with polysorbate 80. Higher serum levels of MTX do not necessarily lead to higher brain levels, indicating that the surfactant has a direct effect on barrier permeability. It is likely that a combination of effects are responsible.

Table 1. Results of administration of MTX with and without polysorbate 80 in mice, 2h after iv administration.

Dosage mg kg ⁻¹		MTX concentration	
(MTX)	(Polysorbate 80)	µg ml ⁻¹ serum	µg g ⁻¹ brain
0.5	0	0.22	0
0.5	3.2	0.13	0.06
0.5	8	0.14	0.21
0.5	32	0.16	0.21
4	0	0.19±0.07	0.07
4	3.2	0.11±0.07	0.14
4	8	0.14±0.01	0.08
8	0	0.42±0.10	0.12±0.03
8	3.2	0.23±0.06	0.15±0.02
8	8	0.17±0.04	0.18±0.06

Azmin, M.N., Stuart, J.F.B., Florence, A.T., Calman, K.C. (1982)
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