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INTERFERON-INDUCING ACTIVITY OF DIPYRIDAMOLE IN MICE

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Summary. — The kinetics of interferon (IFN) production was studied in mice after intraperitoneal (i.p.) and oral administrations of dipyridamole. The substance showed a high IFN-inducing activity when given orally at single doses ranging from 12.5 to 100 mg/kg (1/21.5—1/172 of the single LD_{50} value): peak titres of 2048—4096 IU/ml in the blood serum were reached at 48 hr; elevated IFN levels persisted until day 5 after administration of the inducer. Significantly lower IFN titres were found after i.p. injection.

Key words: *dipyridamole*; *interferon inducer*; *animal model*

Introduction

Dipyridamole (Persantin, Curantyl) was previously reported (Galabov and Mastikova, 1982) to be an IFN inducer. This compound, a well known coronary vasodilatator and antiaggregant, is capable of inducing IFN production *in vitro* in mouse and human lymphoid as well as non-lymphoid cells. Moreover, dipyridamole stimulates IFN production when administered intravenously in mice. Fairly low peak IFN levels of 128 IU/ml could be measured in blood 48 hr post injection of 0.1 mg/kg, 1/1500 of the single intravenous LD_{50} (Galabov and Mastikova, 1982).

Experiments with tilorone and other low-molecular-weight IFN inducers revealed the low efficiency or inefficiency of the intravenous route of administration (Mayer and Krueger, 1970; Krueger *et al.*, 1971; Soehner *et al.*, 1974). These data prompted us to seek for other routes of dipyridamole application, namely i.p. or oral. The results of this study are presented in this communication.

Materials and Methods

Single doses of dipyridamole [2,6-bis(diethanolamino)-4,8-dipiperidinopyrimido-[5,4-d]--pyrimidine] were administered to female albino random-bred mice (H line) weighing 20—25 g. Each experimental group consisted of 49 animals, 7 of which were bled at 6, 12, 24, 48, 72, 96 and 120 hr after drug administration. The control (placebo) group received the solvent only.

IFN titre was determined in pooled serum samples by a micro-variant of plaque-inhibition method (Galabov and Mastikova, 1982) using L cells challenged with vesicular stomatitis virus.

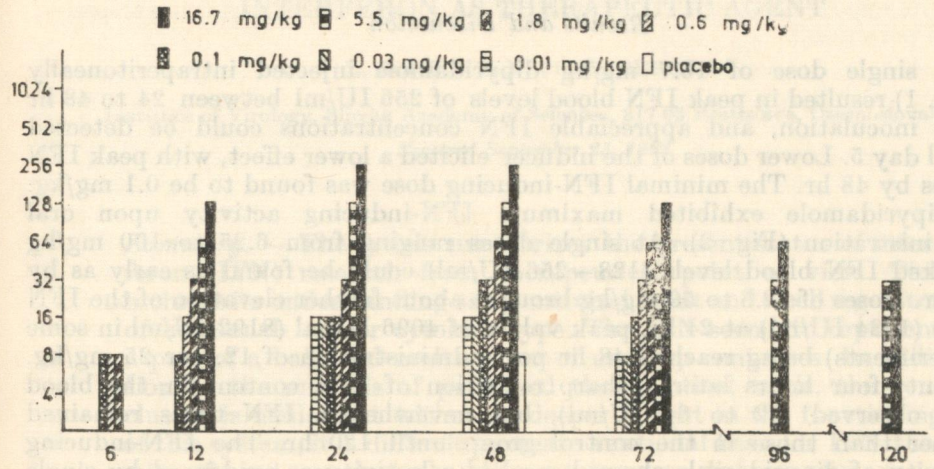

Fig. 1.

IFN levels in mouse serum in response to i.p. injection of single doses of dipyridamole
Abscissa: hr post injection; ordinate: IFN titre in IU/ml.

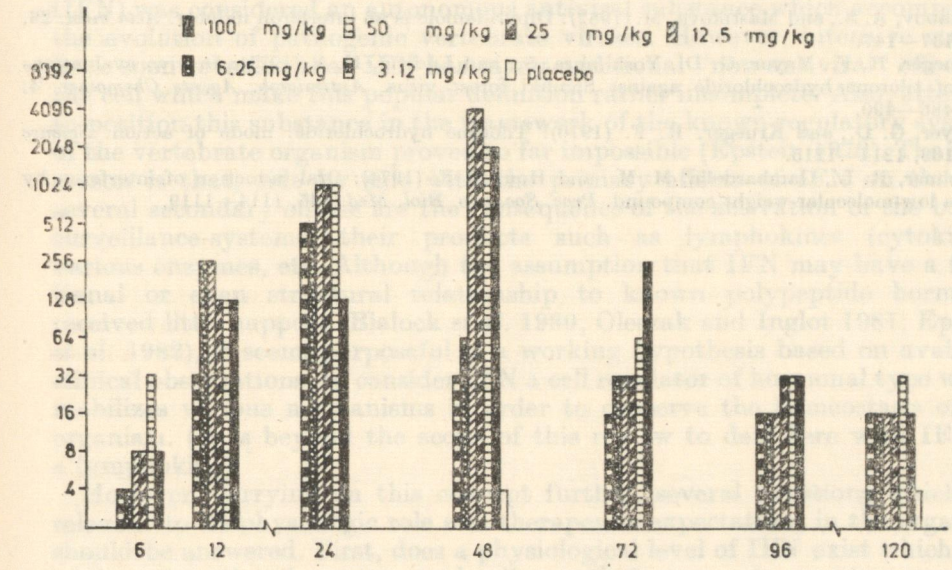

Fig. 2.

IFN levels in mouse serum in response to oral administration of single doses of dipyridamole
Abscissa: hr post injection; ordinate: IFN titre in IU/ml.

Results and Discussion

A single dose of 16.7 mg/kg dipyridamole injected intraperitoneally (Fig. 1) resulted in peak IFN blood levels of 256 IU/ml between 24 to 48 hr post inoculation, and appreciable IFN concentrations could be detected until day 5. Lower doses of the inducer elicited a lower effect, with peak IFN titres by 48 hr. The minimal IFN-inducing dose was found to be 0.1 mg/kg.

Dipyridamole exhibited maximum IFN-inducing activity upon oral administration (Fig. 2). At single doses ranging from 6.25 to 100 mg/kg marked IFN blood levels (128—256 IU/ml) could be found as early as by 12 hr. Doses of 12.5 to 50 mg/kg brought about further elevation of the IFN titre (1024 IU/ml) at 24 hr, peak values of 4096 IU/ml (8192 IU/ml in some experiments) being reached 48 hr post administration of 12.5 or 25 mg/kg. Twenty-four hours later a sharp reduction of IFN content in the blood was observed (32 to 64 IU/ml), but nevertheless, IFN titres remained higher than those in the control group until 120 hr. The IFN-inducing activity of dipyridamole showed marked selectivity as evidenced by single (acute) oral LD_{50}, which amounted to 2150 mg/kg, i.e. the selectivity index ranged within 21.5—689.

These results indicate that dipyridamole administered orally is a potent interferon inducer in mice.

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