The effect of celery and parsley juices on pharmacodynamic activity of drugs involving cytochrome P450 in their metabolism

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SUMMARY

Celery (Apium graveolens) and parsley (Petroselinum sativum), plants used worldwide in human nutrition, are the natural sources of methoxsalen. In this study we investigated the effect of mice pretreatment with juices of this plants on the hypnotic action of pentobarbital and analgesic action of paracetamol and aminopyrine, the drugs involving cytochrome P450 superfamily in their metabolism. In mice pretreated with celery and parsley juices a prolonged action of pentobarbital with respect to control was observed, statistical significance being attained only with parsley-pretreated animals. Both pretreatments increased and prolonged the analgesic action of aminopyrine and paracetamol, pretreatment with parsley being again more effective. Celery and parsley juices given to animals two hours before their decapitation caused a significant decrease of cytochrome P450 in the liver homogenate as compared to control.

INTRODUCTION

The increased use of herbal medicines has been accompanied by an increase in the number of side effects produced by these "drugs". A WHO publication from 1998 pointed out the need to have a regulatory statute for herbal medicines (1).

It is difficult, however, to identify all the side effects of herbal preparations, as herb blends are usually used and the contents of a particular ,,healing,, component varies

Please send reprint requests to: Dr. Vida Jakovljevic, Department of Pharmacology, Toxicology and Clinical Pharmacology. Faculty of Medicine, Hajduk Veljikova 3, 21000 Novi Sad, Yugoslavia as a function of the area of plant growing, climatic conditions, and the like. Thus Finkelstein et al. (2) found a significant difference in the content of psoralen in the rhizome of celery cultivated the same year, depending on whether the plant was grown in the south or north part of Israel. The psoralen content in the celery rhizome from the north was 35 and in that from the south 84 μ g/g fresh plant.

Bursac et al. (3) concluded that even small doses of methoxsalen can have a significant effect on the hypnotic dose of barbiturates. In view of that the objective of this work was to study the interaction of plant juices that are natural sources of methoxsalen and the drugs whose metabolism involves the cytochrome P450 activity was evaluated.

MATERIALS AND METHODS

Laboratory animals and pretreatment

The experiments were carried on NMRI-Haan white laboratory mice of both sexes, b.w. 20-28 g, more than 3 months old. The experimental animals received either a single or multiple dose of parsley or celery juice, whereas the control animals received olive oil and saline. During the experiment the animals had free access to water and food.

Preparation of emulsions and vlumes injected

Expressed celery juice was obtained by pressing the grated rhizome, and the juice was mixed with olive oil (1:1). Single or multiple emulsion doses of 10 ml/kg b.w. were given p.o.

Parsley juice was obtained by pressing the grated root, and it was mixed with water and olive oil in ratio 4:3:3. Either single or multiple doses of 10 ml/kg b.w. of the emulsion were given p.o.

In a repeated pretreatment animals received the above doses of emulsions 24, 4, 2, and 0.5 h before pentobarbital was administered.

Drugs and experimental models

Pentobarbital, in the form of pure substance, was given i.p. to mice in a dose of 40 mg/kg b.w., and the induction and sleeping time were measured (4).

The analgesic effect of aminopyrine (60 mg/kg, i.p.) and paracetamol (80 mg/kg, i.p.) was measured by hot-plate method (4).

Contents of the cytochrome P450 in liver homogenates of mice that received a single dose of parsley or celery juice were measured 2 hours before their decapitation, compared with the control, using the method of Matsubara te al. (5).

Each group consisted of 6 animals.

RESULTS

Sleeping time

Single doses of the emulsions containing celery or parsley juices given 30 minutes before administering pentobarbital did not change significantly the sleeping time compared with that of control animals. However, pretreatment of mice with these emulsions 120 min before pentobarbital extended sleeping time in both groups, the change being



Fig. 1: The influence of single doses of celery and parsley juices given 30 and 120 minutes before pentobarbital.



Fig. 2: The influence of repeated pretreatment with celery and parsley juice on hypnotic effect of pentobarbital.

statistically significant only with parsley-pretreated animals. The results are presented in Fig. 1.

Repeated pretreatment resulted in an extended sleeping time compared to the control, whereby in this case too the extension was statistically significant only in the parsley-pretreated group (Fig.2.).

Analgesimetry

Mice pretreatment with parsley and celery juices two hours before administering analgesics changed significantly the analgesic action of paracetamol and aminopyrine compared with the control.

As can be seen from the Fig. 3, celery and parsley juices both potentiated and prolonged the analgesic action of aminopyrine, the difference with respect to the control attaining statistical significance only in the case of parsley (Fig.3).

A significant effect of mice pretreatment with the investigated emulsions was obtained in the interaction with paracetamol. It is evident from Fig. 4 that the analgesic



Fig. 3 : The influence of celery and parsley juices on analgesic action of aminopyrine.



Fig. 4 : The influence of celery and parsley juices on analgesic action of paracetamol.

effect was intensified most when pretreatment with celery was applied 30 min before injecting paracetamol, whereas in case of parsley this happened in the first measured time (5 min). Both pretreatments resulted in an enhanced and prolonged analgesic action of paracetamol (Fig. 4).

Cytochrome content

Contents of the cytochrome P450 measured in the liver homogenates of control animals and those pretreated with investigated emulsions are presented in Table I.

DISCUSSION

If the influence on the measured pharmacodynamic effects are compared it can be concluded that pretreatment with parsley was more effective in all cases. This is in agreement with the results of Beir et al. (6) whose HPLC studies showed that fresh parsley root contains $112\mu g/g$ of furocoumarin. According to Avalas et al. (7) the psoralen

Table 1: Contents of the cytochrome P450 in liver homogenates of control mice in comparison with those obtained after single pretreatment with celery and parsley juice.

content in fresh celery is in the range of $0.08-0.24 \mu g/g$, whereas other authors (2) reported a content of 35-84 $\mu g/g$, which indicates that the psoralen content in celery may vary in a very wide range.

Ulaterodriguez et al. (8) found that psoralens from celery, parsley and lemon have antibacterial action against Listeria monocytogenes and E. coli. Celery juice in combination with UV radiation showed a dose-dependent and statistically significant mortality of Lepidoptera noctuidae larvae compared to the cintrol (9).

On the bases of the results of this preliminary study of the influence of natural methoxsalen sources on the pharmacodynamic effects of drugs involving the cytochrome P450 in their metabolism it can be concluded that the effect of parsley and celery in the everyday diet should not be neglected because of the possible appearance of interaction or side effects.

Gral et al. (10) presented data showing that no phototoxic changes on the skin appeared with subjects who took 500 g ofcelery, and neither measurable quantities of psoralen were attained in their circulation. However, as the authors mentioned, this observation does not exclude the possibility of the occurrence of phototoxicity with the patients on the PUVA therapy.

CONCLUSIONS

Single pretreatment of mice with parsley 2 hours before administering a hypnotic dose of pentobarbital induced significant extension of sleeping time in mice. The prolonged hypnotic time, however, did not attain statistical significance in case of pretreatment with celery.

Repeated pretreatment (4 doses/24 h) of mice with the investigated emulsions prolonged the hypnotic action of pentobarbital but statistical significance was attained only with parsley-pretreated animals.

Single pretreatment of mice with celery increased and prolonged the analgesic effect (hot-plate results) of aminopyrine, statistical significance being attained only in the interaction with paracetamol. Single pretreatment of mice with parsley juice caused statistically significant increase and prolonged analgesic effect of both aminopyrine and paracetamol.

With the mice receiving a single dose of parsley or celery juice 2 h before their decapitation a statistically significant decrease in the content of the cytochrome P450 in the liver homogenate was observed compared with the control.

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