Interaction of alcoholic extracts of hops with cocaine and paracetamol in mice

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SUMMARY

This work describes a study of the interaction in the mouse model of alcoholic extracts of hops of Magnum, Aroma and wild genotypes with drugs that have excitatory effect on the cerebral cortex (cocaine) and analgesic action (paracetamol). Hop drying and preparation of the extracts were carried out according to standard pharmacological procedures for preparing total alcoholic extracts of dry herbs, consisting of one part of dry drug and two parts of 70% alcohol. The mice received four doses i.p. of 0.5% aqueous solutions of the above-mentioned extracts (10 ml/kg) 24, 16, 4 and 0.5 h prior to receiving cocaine (25 mg/kg) or paracetamol (80 mg/kg). The parameter investigated was the change in spontaneous motility of mice after combined treatment with the extracts and cocaine/paracetamol compared to control animals that received the same dose of the drug after treatment with physiological solution. Only the ethanolic extract of Magnum hops increased the spontaneous motility of mice, while none of the extracts showed analgesic action as measured by the hot-plate method. In the interaction with cocaine, the extract of Magnum hops suppressed almost completely the action of cocaine compared to controls. Extracts of the other hops also decreased the cocaine-induced locomotor activity of mice, but to a lesser extent. Hop extracts exhibited a significant pharmacological interaction with paracetamol, with the most pronounced increase in analgesic action being found for the ethanolic extract of Aroma hops and the tert-butanolic extract of wild hops.

INTRODUCTION

Herbal preparations, used either as an auxiliary remedy or as an alternative to standard drugs, have been increasingly used in modern societies. It is commonly considered that herbal preparations have a lower incidence of undesirable side effects compared to classical drugs, and patients, often without their doctor's advice, may make decisions about the type, mode of administration and dosage of these preparations.

The active principles present in herbal extracts can influence the action of drugs with which they are simultaneously administered, thereby exhibiting significant interactions. Because of this, investigation into the effect of herbal preparations on the pharmacological properties of drugs has attracted the increasing attention of researchers.

Hop (Humulus lupus) is a perennial herbaceous plant whose cones ripen at the end of summer and which are used in brewing to give beer its pleasant and characteristic bitter flavor. It is thought that hop cones (hops) have mild narcotic properties and sedative action, so they were used even in ancient times to treat pain and psychic disorders (1). Today, primarily for the purpose of improving beer characteristics, an extremely large number of hop genotypes
are grown worldwide. Depending on the genotype, hops have different contents of tannins, flavonoids and similar biologically active compounds (2).

Contemporary herbal medicine is concerned with investigating the use of hops for their sedative and mildly hypnotic action, as well as their effect on the functioning of the endocrine system, and their antioxidative and anticarcinogenic properties. Humulon isolated from hops exhibits antifungal and antibacterial action (3).

It is thought that the pharmacologically significant agents in hops are the flavonoids, the activity of which depends on the number and position of the hydroxy, ethoxy and methyl groups in the flavone core, the basic structure of hop flavonoids (4,5).

Phytoestrogens extracted from hops have a beneficial effect on disturbances related to the menstrual cycle in women during the menopause. It is also considered that their administration may reduce the development of breast cancer, as well as the incidence of cardiovascular disorders (6-8).

Regarding recent studies of the influence of hops on the functioning of the central nervous system, it should be mentioned that a comparative investigation has been made of the administration of mixtures of hop extracts and valerian and the effects of benzodiazepines in treating insomnia. The results have indicated identical pharmacotherapeutic effects and good tolerability. Some investigations carried out on animals have also shown that hop extracts potentiate the effects of drugs that have sedative action on the central nervous system (1).

However, in our experiments in mice (9) this action could not be confirmed; in contrast, it was found that the extracts of the investigated hop genotypes suppressed the sedative action of pentobarbital and diazepam.

For this reason, in the present study we investigated the interaction of the above-mentioned extracts of hops with cocaine (as a cerebral cortex stimulator) and paracetamol (an analgoantipyretic).

**MATERIAL AND METHODS**

**Animals**

Experiments were carried out on white laboratory NMRI-Haan mice, body weight 20-30 g. The animals had free access to food and water, and were exposed to a 12-h light-dark cycle at a temperature of 22°C.

Hop extracts as 0.5% of aqueous solution (test animals) or physiological solution (controls) were given to mice 24, 16, 2 and 0.5 h prior to administering cocaine or paracetamol.

**Hop extracts and experimental groups**

Hop was grown in the fields of the Scientific Institute for Field Crops and Vegetables in Backi Petrovac (Vojvodina, Serbia), 2005 harvest. The processes of hop drying and preparation of extracts were carried out according to standard pharmacological procedures for the preparation of total alcoholic extracts of medicinal herbs, in a dry herb/70% alcohol ratio of 1:2. The extract was evaporated to dryness, dissolved in warm physiological solution to make up 0.5% aqueous solutions, with the percentage being related to the total weight of dry hops used for the extraction.

Ethanolic and tert-butanolic extracts of hops of the genotypes Aroma and Magnum as well as those obtained from wild hops were used. The following experimental groups (with 8 mice in each group, i.e. a total number of 56 study animals) were constituted:

1. total ethanolic extract of Magnum genotype (ME)
2. tert-butanolic extract of Magnum genotype (MB)
3. total ethanolic extract of Aroma genotype (AE)
4. tert-butanolic extract of Aroma genotype (AB)
5. total ethanolic extract of wild-growing hops (DE)
6. tert-butanolic extract of wild-growing hops (DB)
7. controls, receiving only physiological solution (C)

**Drugs**

Cocaine hydrochloride (Sigma) was dissolved in physiological solution and injected i.p. at a dose of 25 mg/kg 0.5 h after the last (fourth) dose of extract or of physiological solution.

Paracetamol (acetaminophen) (Sigma) was dissolved in physiological solution and injected i.p. (80 mg/kg) following the same scheme as for cocaine.

**Methods**

**Spontaneous motility of mice**

The spontaneous motility of mice was measured on a DSE Type Animex activity meter (Farod Electronics, Sweden), which enabled all locomotor movements in the animal on the sensory field to be recorded. Two mice were placed under a glass funnel, and their spontaneous motility was measured at predefined time points after cocaine injection, with each measurement lasting 3 min for the given time period.

The mice received doses of 10 ml/kg of 0.5% aqueous solution of hop extracts 24, 16, 2 and 0.5 h prior to cocaine administration, and 15 min after the fourth