CONTENTS

1. THE DUAL ROLE OF L-ARGININE IN NOCICEPTIVE PROCESSING: L-ARGININE-KYOTORPHIN SZSTEM VERSUS L-ARGININE-NITRIC OXIDE PATHWAY

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ABSRTACT
The role of L-arginine in nociceptive processing was assessed using different acute pain models: tail-flick, hot-plate, algesimetric and writhing assay. Different groups were treated with 1) L-arginine (i.p. 1000 mg/kg, i.t. 1 mg/rat), 2) association of L-NG-nitroarginine methyl ester (L-NAME, i.p. 75 mg/kg, i.t. 0,1 mg/rat) with L-arginine, 3) L-ornithine (i.p. 1000 mg/kg). The 1000 mg/kg i.p. dose of both L-arginine and L-ornithine induced an analgesic effect on mice in the hot-plate and writhing assay, but did not alter the tail-flick latencies. This anti-nociceptive effect was significantly antagonized by prior subcutaneous administration of naloxone. L-arginine administred i.t. on rats tends to induce an increase of response latency to nociceptive stimuli for algesimetric and tail-flick tests. These results suggest an antinociceptive action of L-arginine, possible through kyotorphin system. The antinociceptive effect of L-arginine is increased in association with L-NAME, an nitric oxide (NO) synthase inhibitor, so it appears that the possible pro-nociceptive influences of L-arginine mediated through the NO synthase/NO/cGMP cascade are surpassed by the analgesic action of L-arginine through L-arginine-kyotorphin system.

Key words: L-arginine, nociceptive, processing, nitric oxide synthase, nitric oxide.

2. THE EFFECTS OF NITRIC OXIDE ON AIRWAY RESPONSIVITY IN HEALTHY AND OVALBUMIN SENSITIZED RATS

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ABSTRACT
Objectives: Nitric oxide (NO) donor, glyceryl trinitrate (GTN) and NOS inhibitor N^{w}-nitro-L-arginine (L-NA) were used to investigate the role of NO in airways responsiveness of healthy and asthmatic rats.
Material and method: The experiments were performed on 4 groups or Sprague-Dowley adult rats: group I – control; group II – ovalbumin sensitized rats; group III – ovalbumin sensitized rats treated

with montelukast, a synthetic leukotriene receptor antagonist; group IV – ovalbumin sensitized rats treated with glucocorticoids. Tracheal spirals were introduced in organ chambers filled with Krebs-Hanseleit solution, bubbled with 95% O_2 and 5% CO_2, at 37^o C. isometric force was measured using a force transducer and the results were recorded using a computerized data acquisition unit. Airways responsiveness to a muscarinic agonist, acetylcholine, was measured. The bronchodilator action of NO was evaluated by administration GTN, with or without a previous pre-contraction of the preparations with acetylcholine. The effect of L-NA was assessed in two situations: after pre-contraction of the preparations with acethylcholine, and also on the basal tone (incubation of the preparation with L-NA) followed by administration of the muscarinic agonist.
Results: In ovalbumin-sensitized rats, reduced contractile reactions were noticed, but the basal tone was significantly higher. In animals treated with either montelukast or glucocorticoids, the improvement of basal relaxation was correlated with higher acethylcholine-induced contractions. GTN was a weak bronchodilator, its relaxing action being abolished by ovalbumin sensitization, and restored after treatment with either montelukast or glucocorticoids. In our experiments, L-NA alone induced a contractile action in almost all groups, except SO group, in which no contraction was observed. Corticotherapy, and especially montelukast augmented the contractile action of L-NA.
Conclusions: Administration of exogenous NO induces weak relaxing effect in all studied animals, its effect being annulled by ovalbumin sensitization and restored by therapy with either antileukotrienes or glucocorticoids. Montelukast potentates the contractile effect of the NOS inhibitor, suggesting that cNOS might play an important role in the development of bronchial hyperreactivity. Thus, its action seems to be more pronounced compared to that induced by corticotherapy, which decreases iNOS activity.

Key words: tracheal smooth muscle, Sprague-Dowley rats, ovalbumin, sensitization, nitric oxide.

3. EFFECTS OF SOME VASODILATORS ON KCL-INDUCED CARDIAC ARRHYTHMIAS. EXPERIMENTS CARRIED OUT BY INTRATECHAL ADMINISTRATION IN ANESTHETIZED RATS

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ABSTRACT
In pentobarbital-anesthetized rats, the intrathecal (i.t.) administration of KCl induces bradycardia and cardiac arrhythmias. Vinpocetine, dipyridamole, and papaverine given i.t. had a small effect on the slowing down of the heart rate, but they blocked quasicompletely the cardiac arrhythmias.

Key words: rats, intratechal, heart rate, arrhythmias, KCl, dipyridamole, papaverine, vinpocetine.

4. MATHEMATICAL METHOD FOR CANCER-RELATED GENES DISCOVERY BY MICROARRAY DATA ANALYSIS

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ABSTRACT
In this paper we introduce a new mathematical method for selecting cancer-informative genes from microarray data. Usually, genes of interest are selected by ranking genes according to a test statistic and then choose the top genes. However, the main problem with this approach is that most statistical

tests assume a normal distribution of the data, which is frequently not the case. To identify cancer-related genes, it would be ideal to have distinct but still highly informative genes. One of the most valuable techniques currently utilized is discriminate analysis (supervised learning). A key issue to improve the classification performance is to find the genes that are most likely to contribute to the separation of the types (classes) of tissues (or diseases), because not all the genes are needed for the discriminant analysis. In this paper, we introduce a new method for gene selection, based on the theory of sets. The method substantially improves the performance of the acute leukemia classification based on microarray data (presented in Golub et al.), using both symbolic and subsymbolic machine learning algorithms.

Key words: cancer-related genes, microarray data analysis, featutre selection, machine learning.

5. QSAR FOR ECOTOXICOLOGY: THE EXPERIENCE OF THE TIMISOARA GROUP

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ABSTRACT
An enormous number of organic and inorganic chemicals are potential pollutants, due both to their toxicity, and to high persistence in nature. A non-specific action is observed for large classes of substances (alcohols, aldehydes, etc.) determined largely by hydrophobicity, but several pollutants act upon specific receptors. The interest for QSAR studies in this domain is obvious.
The Timisoara group of QSAR has performed Hansch type QSAR studies for the toxicity on mammals of organophosphorus pesticides already in the seventies. In the last ten years, QSAR studies were performed on a large series of mutagenic aromatic amines, using a modified, classical MLR-method such as to include also inactive substances. Another QSAR study by the MLR method, combined also with PLS, was performed for a large series of inorganic cations, with an attempt to introduce also nontoxic cations. 3D-QSAR methods, namely MTD and PLS variant of MTD were performed for a series of over 70 polyhalogenated derivatives of dibenzoxine and diphenyl.
The studied substances interact with specific receptors. The QSAR results are modest for the series of mutagenic aromatic amines and especially for the series of inorganic cations; different molecules (ions) of these series probably act upon different receptors. The results are very good for the series of polyhalogenated aromatic derivatives; their toxicity is probably based upon interaction with the same receptor.

Key words: QSAR studies, MTD-method, polyhalogenated derivatives, mutagenic aromatic amines, inorganic pollutants.