Review of Clinical Pharmacology and Pharmacokinetics

EPITHEORESE KLINIKES FARMAKOLOGIAS KAI FARMAKOKINETIKES
ΕΠΙΘΕΩΡΗΣΗ ΚΛΙΝΙΚΗΣ ΦΑΡΜΑΚΟΛΟΓΙΑΣ ΚΑΙ ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΗΣ
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GENERAL INFORMATIONS

REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

publishes Applied Pharmacology and Current Therapeutics Reviews, Review Articles on Drugs and Drug Therapy, Original Papers and Practical Therapeutics Articles.

The *scientific standard* of the papers, which are accepted for publication, is controlled by the Editorial Board or by other Experts in the various fields of Pharmacology and Pharmacokinetics.

Manuscripts: These should mention, on the first page, the *Title*, *Author(s)* and the *Name of the Institution* at which the work was done. The complete *address* of the author, including Postal area code number, should be given under the rubric *Send reprint requests to*. Papers should follow the general form: *Introduction, Materials and Methods, Results, Discussion* and *References*. Drugs must be referred to by their generic or chemical name, but may be identified by trade name in parenthesis or o footnote. All papers should be submitted in duplicate.

Summary: A summary in English (maximum length 200 words) must accompany all manuscripts.

Key words: A list of key words should be submitted.

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Papers should be submitted to the Editors-in-Chief: Prof. S.T. Plessas or Dr C.T. Plessas.

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INVITED SPEAKERS

ORAL AND POSTERS PRESENTATIONS

Letter from Guest Editor

The progress and contributions of 20th century pharmacology has been immense with over 20 pharmacologists to have received Nobel Prizes. This field of medical studies covers many areas; it is built upon and at the same time incorporates many disciplines such as biochemistry, biology physiology, pathology, anatomy, molecular biology, while the development of new analytical and experimental techniques and instruments has given a new boost in pharmacological research. Yet, although a remarkable progress has been made in developing new drugs and in understanding how they act, the challenges are endless. Integrating a depth of knowledge in many related scientific disciplines, pharmacologists offer a unique perspective to solving drug and chemical related problems which impinge on human health, with ultimate goal the treatment and prevention of major diseases.

The 5th Panhellenic Congress of Pharmacology focuses on four *hot* subjects: Regenerative Pharmacology, Herbal Medicines, Pharmacology of Abuse and Dependence, and Education in Pharmacology.

- *Regenerative Pharmacology* is one of the newest areas in Pharmacology, represents a groundbreaking field of research and has the potential to radically alter the treatment of diseases and disorders.

- *Herbal Medicines* have acquired an important percentage among the drug used; according to WHO 80% of people worldwide rely on herbal medicines for some aspect of their primary health care. This continuously increasing use of plant medicines imposes the need for establishing new regulations.

- *Pharmacology of Abuse and Dependence*, still not a well defined area, presents a lot of challenge for researchers and clinicians.

- *Education in Pharmacology* remains a hot subject in the Medical education, following the knowledge *explosion* of the last decades accompanied by a decreasing reliance on didactic teaching. The crucial question is: how and what should we teach?

We hope that the round table discussions along with the invited lectures, included in this abstract book, will raise new and intriguing ques-

tions that will further stimulate research, and will contribute to new therapeutic approaches and attitudes.

I would like to thank the Editorial Board of *Review of Clinical Pharmacology and Pharmacokinetics* in particular Journal Editors Prof. S.T. Plessas and Dr C.T. Plessas for invitation and for providing the suitable and high-standard forum through which new research findings will become available to the scientific community.

The Guest Editor

Charis Liapi

Assist. Professor in Pharmacology
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Chair of Hellenic Society of Pharmacology

REVIEW OF CLINICAL PHARMACOLOGY AND
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Acute *in vivo* Exposure to Fentanyl Reduces GABA Immunoreactivity in the CA1 Area of the Rat Hippocampus

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Key words: Opioids, hippocampus, excitability, immunoreactivity

S u m m a r y. The effect of in vivo fentanyl treatment on GABAergic immunoreactivity was studied in the CA1 area of the rat hippocampus. Animals were treated either with saline or fentanyl (4×80 μg/kg, s.c./15min). GABA immunohistochemistry revealed lower GABA content in processes and neuronal somata suggesting reduced GABA release onto pyramidal neurons. Thus, acute in vivo exposure to fentanyl may result in a long-lasting alteration in the excitability within the CA1 area of the hippocampus. These findings are in line with previously reported reduced GABA mediated transmission and may provide evidence regarding mechanisms involved in the early stages of tolerance development towards the analgesic effects of opioids.

INTRODUCTION

In vitro activation of opioid receptors in the hippocampus, located solely on interneurons (1), hyperpolarizes inhibitory interneurons (2) and inhibits the release of GABA from interneuronal terminals (3). Therefore, the excitatory response to opioids is considered to be an indirect effect, due to a disinhibitory process. The aim of the present study was to examine the effect of *in vivo* administration of fentanyl on GABA immunoreactivity in the CA1 area of the hippocampus.

METHODS

Adult male Wistar rats 250-300 g were housed three to four per cage with free access to food and water. Rats were randomly selected and divided into animals treated with saline and those treated with fentanyl (4 injections, 20 or 80 μg/kg per injection, subcutaneously, every 15 min) resulting in total dose 80 and 320 μg/kg. 24 hours after saline (n=4) or fentanyl (n=5) treatment they were deeply anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and transcardially perfused with 4% paraformaldehyde. After fixation, brains were incubated in 30% sucrose for cryoprotection. Tissues were subsequently frozen in isopentane (-45 ^{o}C, 1 min) and kept at -80 ^{o}C. Slices, 10 μm thick, were cut coronally with a cryostat at the level of hippocampus and stored at -20 ^{o}C. The presence of GABAergic neurons in the tissue was assessed immunohistochemically using a polyclonal rabbit antibody against GABA. Data were expressed as mean ± S.E.M (in all cases *n*=number of neurons) and were analyzed statistically using the unpaired Student's *t* test.

RESULTS

Acute *in vivo* fentanyl treatment did not alter the number of neuronal cell bodies expressing GABA (saline: 4.8±1.2; fentanyl: 5.0±0.9; $p>0.05$). However, GABAergic immunoreactivity was decreased 24h after drug administration. The mean fluorescence intensity measured in the total image was significantly lower (45.9%) in brain sections from fentanyl-treated animals (saline: 5.1±0.4, n=4; fentanyl: 2.8±0.2, n=4; $p<0.001$). Furthermore, fentanyl treatment resulted in marked reduction (62.2%) of the maximal value of fluorescence intensity detected in the whole image (saline: 75.3±13.8, n=4; fentanyl: 28.5±3.7, n=4; $p<0.05$).

DISCUSSION

GABA immunohistochemistry revealed that *in vivo* fentanyl treatment leads to lower GABA content in processes and somata, suggesting reduced GABA release onto pyramidal neurons. We conclude that a single *in vivo* exposure to

fentanyl is sufficient to induce long-lasting reduction in GABA-mediated transmission. These findings are in line with the enhancement of excitatory transmission after *in vitro* opioid (4-6) treatment and may provide evidence regarding the mechanisms involved in the early stages of tolerance development towards the analgesic effects of opioids.

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