substrate, however, there are relatively little data about the role of (−)R and (+)S isomers in the neurotoxicity

Aim of the present experiments was to follow the behavioural consequences (locomotor activity and 5-HT syndrome) of (−)R and (+)S-MDMA enantiomers induced neurotoxicity in rats.

Methods: 4×10 mg/kg (+) MDMA and 4×20 mg/kg (−) MDMA sc. in every 2nd hour was used to induce the neurotoxicity. The general motor activity was checked in an Activity Animal Measurement System where both the horizontal activity (ambulation) and the vertical one (rearing) were observed simultaneously in novel surroundings. Intensity of 5-HT-syndrome was evaluated by checking the appearance of three stereotyped parameters (hindlimb abduction, forepaw treading and Straub tail). Body temperature and body weight were measured 30 min after the last injection; spontaneous motor activity was checked 3 days after it. The intensity of the (+) and (−) MDMA challenge induced behavioural effects were followed on the 3rd, 14th and 28th posttreatment day.

Results: (+)S MDMA in neurotoxic regimen significantly increased the body temperature and reduced the body weight. Spontaneous motor activity was significantly inhibited on the 3rd posttreatment day, however this inhibition was not detected later. The intensity of both (+) and (-) MDMA challenge (10 mg/kg sc.) induced behavioural activity was significantly lower in the (+) MDMA pretreated animals. (−)R MDMA in neurotoxic regimen, however, failed to affect the body temperature and the body weight and did not provoked inhibition of the spontaneous activity. In due corresponding with these data no change in the challenge-induced behaviour was observed.

Conclusion: Our results indicate that the neurotoxic action of MDMA enantiomers is different. While (+) MDMA proved to induce a marked neurotoxicity, the (-) MDMA in the applied dose failed to do it. According to biochemical data (+) MDMA is more potent 5-HT releaser, than the (-) enantiomer (2). This discrepancy might be responsible for the significant difference capacity to induce neurotoxicity.

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P.5.016 Antisocial personality disorder–heroin-dependence comorbidity

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Background: About 60%-80% of heroin-dependent patients are diagnosed with a comorbid psychiatric disorder; among these,the personality disorder diagnosis has the highest rate of occurrence.

Objective: To examine heroin-dependent patients with comorbid antisocial personality disorder, considering family background, educational level, withdrawal syndrome severity index, Lowenstein-Gourarier score, somatic and psychiatric complications and relapse phenomenon.

Method: 70 patients with antisocial personality disorder and heroin-dependence, according to DSM IV criteria, were followed up for 5 years after admission for heroin-withdrawal syndrome.

Assessments: Clinical evaluations, withdrawal syndrome severity index, Lowenstein-Gourarier score, urine analysis, HIV and viral hepatitis tests.

Results: 71% of patients had low educational level, they came from disorganised (57%) or dysfunctional (29%) family environment or from institutional environment(14%); 54% were admitted in stage IV of withdrawal syndrome and most of them presented in stage D (57%) and C(29%) of Lowenstein-Gourarier score.

The most frequent psychiatric complications were: confusional syndromes, depressive disorders, anxiety disorders and amotivational syndrome.

The most frequent somatic complications were C and B viral hepatitis, HIV and pulmonary tuberculosis. Relapse rate was 100%, meaning that all patients with antisocial personality disorder relapsed in heroin-consuming after withdrawal.

Conclusions: Antisocial personality disorder represents a negative predictive factor for heroin-dependence outcome, due to higher rate of complications and heroin-consuming relapse.

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P.5.017 Behavioural effects of some non-quaternary ionisable derivatives of 14-methoxymetopon in rats

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Ionisable derivatives of the mu-opioid receptor selective 14-methoxymetopon were synthesised for the purpose of searching strong analgesic compounds with smaller or minimized central effects (1,2).

Aim of the present study was to analyse the antinociceptive action and some behavioural effects of two of the most promising compounds and compare them to the effects of morphine (MO).

Methods: The antinociceptive action was measured by tail-flick test, the proportion of the central versus peripheral actions was determined by subcutaneous (s.c.) ED50/intracerebroventricular (i.c.v.) ED50 ratios. For investigating the behavioural effects the compounds were administered s.c.. The general motor activity was checked in an Activity Animal Measurement System where both the horizontal activity (ambulation) and the vertical one (rearing) were observed simultaneously in novel surroundings. The conditioned reinforcement was measured with the aid of conditioned place preference (CPP) paradigm. Two mu-opiod receptor agonist derivatives were studied, HS-731 and HS-730, which were found in the mouse vas deferens bioassay to be highly potent (IC50=7.0±0.79 nM) and potent (IC50=26.8±3.63 nM), respectively.

Results: The antinociceptive ED50 s.c. value in rats was 1.9 mg/kg for MO, 86 microg/kg for HS-730 and 28 microg/kg for HS-731, while the i.c.v. ED50 values were 12 microg/rat, 59 ng/rat and 50 ng/rat for MO, HS-730 and HS-731, respectively. The s.c./i.c.v. ratios based on these results were calculated 19, 175 and 67 for MO, HS-730 and HS-731, respectively. The antinociceptive effect of HS compounds given s.c. lasted 2 hours, while it lasted 3–4 hours following i.c.v. administration. Based on these results a dose of 100 microg/kg s.c. was chosen to check the behavioural effects of HS compounds. Administration of MO and HS-730 resulted in a marked conditioned place preference, while HS-731 failed to do it. Similar results were obtained concerning the motor activity, HS-730 significantly decreased the motor activity, HS-731, however, failed to affect it. MO in doses of 1–2 mg/kg induced conditioned place preference and in a dose of 3 mg/kg reduced the motor activity.

Conclusion: The newly synthesised, highly potent mu-opioid receptor agonist HS-731, penetrating poorly to the brain, as indicated by the high s.c./i.c.v. ratio, might be a promising analgesic compound having less central effects and no or smaller addictive properties.

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P.5.018 Involvement of NMDA receptors in alcohol-mediated behavior: Mice with reduced affinity of the NMDA R1 glycine binding site display reduced sensitivity to ethanol

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Ethanol antagonizes central effects of glutamate by inhibition of the NMDA receptor function. The co-agonist glycine has been shown to reverse alcohol-mediated effects. We investigated effects of alcohol administration and withdrawal in mice with a fivefold reduced affinity of the NMDA R1 subunit for glycine (Grin1D481N). Free-choice and forced alcohol intake was studied over a period of 52 days. Exploratory behavior (elevated plus maze, open field) and motor coordination (rotarod) was tested after three days of forced alcohol intake and during ethanol withdrawal.

In contrast to wildtypes, in Grin1D481N mice alcohol-associated anxiolysis and motor impairment was attenuated during intoxication.

However, after onset of withdrawal, Grin1D481N mice exhibited elevated anxiety levels compared with wildtypes. Free-choice alcohol intake did not differ between both groups. Our results give first evidence *in vivo* for a key role of the NMDA-receptor glycine binding site for behavioral alcohol mediated effects.

P.5.019 EuropaASI and opioid dependence pharmaceutical treatment

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Objective: Substance dependence, especially heroin addiction, became after 1991 a very important medical, social and legal issue in Romania. The first step towards abstinence, detofication plays a special part in drug-addicted patient treatment. This study establishes the way EU-ASI test (EuropaASI-index of addiction severity) is to be used in the opioid dependence pharmaceutical treatment's orientation.

Method: A total of 63 drug addicted patients, meeting DSM IV criterias for substance dependence, were given EU-ASI test, in their first day of hospitalization in the Detoxification Center within Al. Obregia Hospital, Bucharest, Romania. 25 patients scored below 6 points on EU-ASI test, the other 38 scored above 8 points. After being tested, specific medication was administered.

Results: Patients with EU-ASI scores above 8 were given: Clonidina, 4cpr. daily (1cpr. = 100 mcg) Metotrimeprazin, 4cpr. daily (1 cpr. = 100 mg) and 4 phials (1 phial = 1ml = 25 mg) Fenpiramid (1 phial = 5ml), 8 phials daily Metoclopramid (1 phial = 2ml), 8 phials daily Diazepam (1 phial = 2ml = 10 mg, 1 cpr. = 10 mg), 4 phials daily and 4cpr. daily. Mean maintenance treatment period was 6 days.

Patients with EU-ASI scores below 6 were given: Clonidina, 4cpr. daily (1 cpr. = 100 mcg), Metotrimeprazin, 8cpr. daily (1 cpr. = 100 mg), Fenpiramid (1 cpr. = 0.1 mg), 8 cpr. daily, Metoclopramid (1 cpr. = 10 ml), 8 cpr. daily, Diazepam (1 cpr. = 10 mg), 8 cpr. daily, for a mean period of 3 days, without the necessity of parenteral medication.

Conclusions: The patients with EU-ASI score above 8 needed high dosage of medication in order to control the withdrawal syndrome symptoms, for a mean period of 6 days. In contrast with these patients, those scoring below 6 points on EU-ASI test needed lower dosage of medication, for a mean period of 3 days. The EU-ASI test can be used in order to chose an adequate, personalised dosage for each drug addicted patient, according with addiction's severity, measured by EU-ASI test.

P.5.020 Effects of the different population densities in the home cage on behavioral sensitization induced by repeated administration of ethanol

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Behavioral sensitization is characterized by a progressive increase of a behavioral effect as a result of repeated administration of a drug. Several evidences have demonstrated that this phenomenon, besides representing a valuable instrument for the study of neuronal plasticity, could provide an important animal model for the study of pharmacological dependence. Indeed, both sensitization to the locomotor stimulating effect and the reinforcement properties exhibited by different drugs of abuse appear to share physiopharmacological features and the same neuronal substrata. In this respect, the study of factors which are able to modify the process of behavioral sensitization may bring relevant information about mechanistic and therapeutic aspects as well. Our aim