ADDICTIVE DISORDERS:
PM283 – PM333

PM283
Agmatine prevents morphine-induced glial activation in rats
Feyza Aricioglu¹, Aydın Sav²
¹Marmara University, Faculty of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul
²Marmara University, Faculty of Medicine, Department of Pathology, Istanbul

Abstract
Objectives: Opioid addiction is associated with long-term adaptive changes in the brain that involve glial activation. Agmatine is an amine formed by the decarboxylation of l-arginine by the enzyme arginine decarboxylase. It binds to α2-adrenergic and imidazoline receptors, and selectively blocks N-methyl-D-aspartate receptors. Agmatine treatment was reported to have various biological actions. It reduces tolerance to morphine and attenuates behavioral signs of morphine in naloxone-induced abstinence syndrome in vitro and in. This study has been designed to evaluate the effect of agmatine on morphine-induced glial activation in rats.

Methods: Male Wistar Albino rats (190–240 g) were divided into three groups such as Control, Morphine and Morphine+Agmatine. Morphine and Morphine+Agmatine groups were received two morphine pellets containing 75 mg morphine base each that was implanted subcutaneously in the scapular area under light anesthesia. Morphine+Agmatine group received agmatine (40 mg/kg, i.p.) and the injection was repeated after 6 hours. 72 hours later naloxone 2 mg/kg i.p was injected to precipitate withdrawal syndrome, observed for 30 minutes and withdrawal symptoms were recorded. Control group received placebo pellets and only saline injections in the same volume of agmatine. Immunohistochemistry was performed to investigate the expression of glial fibrillary acidic protein (GFAP) as indicator of glial activity and c-fos.

Results: Morphine withdrawal syndrome became more severe as it is repeated. When coadministered with morphine, agmatine significantly attenuated withdrawal symptoms. Immunohistochemistry with GFAP revealed that agmatine significantly decreased morphine-induced over-expression of GFAP and c-fos.

Conclusions: Exogenously applied agmatine can prevent morphine-withdrawal-induced glial reactivity and c-fos. As an endogenous molecule agmatine might be a part of compensatory mechanism within the reward pathway. Therefore further studies are required for better understanding the involving mechanisms in order to develop novel approaches for the morphine addiction strategies.

PM284
Agmatine prevents learning and memory deficit in repeated morphine withdrawal: Is it via glutamatergic system?
Feyza Aricioglu¹, Aydin Sav²
¹Marmara University, Faculty of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul
²Marmara University, Faculty of Medicine, Department of Pathology, Istanbul-Turkey

Abstract
Objective: Morphine is important not only because it’s known as a most powerful analgesic but also with its potential for addiction. Withdrawal syndrome which occurs with an absence of morphine is a condition that addicts suffer over and over lifelong. We have previously showed that repeated withdrawal syndrome impaired learning-memory. Current study designed to evaluate possible effect of agmatine treatment on impaired learning-memory and if it is related with glutamatergic system.

Material and Method: Wistar Albino rats were divided into groups such as Control, Morphine and Agmatine+Morphine (n=8 for each group) and subcutaneously implanted with two pellets, 75 mg morphine base containing/each. 72 hours later naloxone 2 mg/kg i.p was injected to precipitate withdrawal syndrome, observed for 30 minutes. This procedure was repeated by implanting one more pellet each time, repeated 6 times and waited for 3 weeks. Animals received 40 mg/kg agmatine twice daily. Animal were undertaken for Morris water maze and passive avoidance tests. Brains were used to evaluate glutamate immunoreactivity.

Results: Morphine withdrawal syndrome became more severe each time and learning-memory functions were impaired by repeating the syndrome. Agmatine treatment prevented learning-memory deficits in Morris water maze and passive avoidance tests. In hematoxylin-eosin stained slices, dark eosinophilic
neurons with red stoplasma were denser in sectors than the other neurons. Glutamate immunopositivity has detected in hippocampal neurons, neuropil, habenular nuclei and cortical tractus. Number of neurons were significantly less in morphine group compared to controls and there were no significant difference between control and agmatine treated groups.

**Conclusion:** According to the findings of the current study repeated morphine withdrawal syndrome can cause damage on learning-memory and glutamatergic system may play a role at least a part. Agmatine has a clear protective role on memory functions. Further research is necessary to understand the mechanism underlying.

**PM285**

Neuropharmacological effect of ketamine-induced hyperlocomotion modulated by age in the C57BL/6J mice

Yi-Chyan Chen M.D., Ph.D.
Department of Psychiatry, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taipei, Taiwan

**Abstract**

**Background:** Ketamine, an antagonist on N-methyl-D-aspartate (NMDA) receptor, can produce neurobehavioral changes ranging from mood alterations and psychotic episodes in human to hyperactivity and stereotyped motion in mice. In the study, we tested the pharmacological properties of ketamine on anxiety, locomotion and motor activity.

**Materials and Methods:** Subjects were C57BL/6J mice with age of 6 and 12 weeks at the time of testing. Mice were housed in a temperature- and humidity-controlled vivarium under a 12 h life-dark cycle with ad libitum access to food and water. Sensitivity to acute intoxicating effect was assessed using accelerating rotorod under given doses of ketamine (0, 10, 25, 50mg/kg, respectively). The elevated plus-maze (EPM) was used to evaluate the anxiety-like behaviors. Open field with videotracking system was adapted to measure the motor responses following acute and chronic ketamine injections.

**Results:** The results demonstrated that the ketamine could dose-dependently potentiate the motor ataxia and significantly increased the open-arm entries at the dose of 25mg/kg through EPM assessment. Ketamine produced hyperactivity at the age of both 6 and 12 weeks. The adolescent mice significantly increased the total moving distance and speed compared to the adult group.

**Conclusion:** These findings suggest that the effect ketamine is regulated by age and potentiating the sensitivity in the adolescent mice.

**PM286**

Cocaine modifies preference of choice in rat gambling task

Bo Ram Cho, Wha Young Kim, Myung Ji Kwak, Jeong-Hoon Kim
Department of Physiology, Brain Korea 21 Plus Project for Medical Science, Yonsei University College of Medicine, Seoul 03722, Korea

**Abstract**

**Background and aims:** Rat gambling task (rGT) is one of the most sophisticated animal model which shares many of the features of the human gambling tasks including uncertainty, reward and punishment. In this model, how cocaine affects the preference of choice has been examined.

**Methods:** Rats were trained in a touch screen chamber to learn the relationships between 4 different light signals on the screen and accompanied reward outcomes and punishments set up with different schedules, for one session of 30min each day. Then, they were allowed for free choices out of 4 different light signals. Once animals showed a stabilized pattern of preference, they were given 7 days of either saline or cocaine IP injections (a single injection per day) followed by 2 weeks of withdrawal. Then, their preference of choice was re-tested in rGT chambers.

**Results:** Depending upon their preference of choice, rats were separated as either risk-averse or risk-seeking groups. However, when they were exposed to cocaine, rats in the risk-averse group significantly changed their preference toward more disadvantageous choices.

**Conclusions:** These results indicate that cocaine influences even different types of decision-making behavior as in gambling task, which is not directly relevant with obtaining cocaine itself, implying that they may aggravate pathological symptoms of bad choices, resulting in negative consequences, observed in the patients with behavioral addictions.

**Keywords:** pathological gambling, cocaine, decision making, behavioral addiction

**PM287**

Mixtures of opioid receptor agonists and cannabinoid receptor agonists: enhanced antinociception without abuse liability

Charles P France, David R Maquire, Vanessa Minervini
Department of Pharmacology, University of Texas Health Science Center, San Antonio, Texas USA

**Abstract**

Mu opioid receptor agonists remain the drugs of choice for treating moderate-severe pain despite their well-documented adverse effects (constipation, respiratory depression, abuse). Kappa opioid receptor agonists also have antinociceptive effects although adverse effects (dysphoria, hallucinations) have precluded their use in the clinic. One strategy for reducing or avoiding the adverse effects of opioid receptor agonists (mu and possibly kappa) is to combine them with drugs that exert antinociceptive effects through nonopioid mechanisms. The need for much smaller doses of each drug in a drug mixture, to achieve the desired therapeutic effect, has the potential to avoid the adverse effects that occur with larger doses of either drug administered alone, thereby increasing the therapeutic window of both drugs. These studies used adult male rats to examine the antinociceptive effects of mu and kappa opioid receptor agonists, each administered alone and in combination with a cannabinoid receptor agonist. When administered alone (intraperitoneally), morphine (mu receptor agonist; 1.78–17.8mg/kg), spiradoline (kappa receptor agonist; 1–32mg/kg), Δ9-tetrahydrocannabinol (THC; cannabinoid receptor agonist; 3.2–32mg/kg), and CP55940 (cannabinoid receptor agonist; 0.032–1mg/kg) increased tail withdrawal latency in a dose-related manner. Mixtures of an opioid and a cannabinoid, in ratios of 3:1, 1:1, and 1:3, also increased tail withdrawal latency from 50°C water in a dose-related manner. Mixtures of some ratios of some mixtures. Together these results support the view that mixtures of opioids and nonopioids could provide significant therapeutic effects (for treating pain) in the absence of some ratios of some mixtures.