DRUG ABUSE: PHARMACOLOGICAL, TOXICOLOGICAL AND CLINICAL ASPECTS

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ABSTRACTS

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Pregabalin-morphine interaction – good or bad in addiction

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Gabapentinoid, pregabalin, is a widely prescribed drug to treat neuropathic pain and generalized anxiety disorder. Pregabalin is believed to have a low abuse potential, but it is also known to produce an euphoric state and misuse in some patients, who have a history of opioid abuse. The conditions and underlying mechanisms of the intereactions of pregabalin and opioids in affecting the reward system have not been investigated. The goal of this study was (1) to determine whether pregabalin alone induce persistent neuroadaptations in the dopamine (DA) reward system and (2) to model possible conditions resulting in increased reinforcing properties of pregabalin. Pregabalin (50-200 mg/kg, i.p.) alone did not induce persistent glutamate neuroadaptation of DA neurons in the ventral tegmental area (VTA), as the AMPAR/NMDAR ratios in VTA DA neurons ex vivo were unaltered 24 h after treatments. Mice did not i.v. self-administer it more than saline. Interestingly, pretreatment with pregabalin suppressed morphine (10 mg/kg, s.c.) treatment-induced neuroplasticity in the VTA DA neurons, attenuated morphine-induced hyperlocomotion and i.v. self-administration of morphine. On the other hand, pregabalin administered after the low-dose morphine treatment (1-3 mg/kg, s.c.) drastically enhanced reinforcing properties of morphine seen as an increase in AMPAR/NMDAR ratio in VTA DA neurons and increased conditioned place preference. Our results are consistent with low abuse potential of pregabalin, when used alone or prior to morphine. However, it should be used with caution, when morphine is on board.

New doping agents and current challenges in anti-doping work

Olavi Airaksinen

Doping can improve athletic performance, but it can also cause severe damage to an athlete's health. The use of doping is contrary to athletic ideals. The main tasks of WADA are as follows:

- to harmonize, develop and maintain WADA's Anti-Doping Code and monitor how various parties comply with it
- to publish and distribute an annual list of substances and methods prohibited in sports
- to develop regional anti-doping programs
- to manage an extensive international research programs
- to accredit doping laboratories
- to carry out an independent international testing program
- to draw up international education and communication programs
- to carry out an independent doping control monitoring programs at major international sports competitions

The main prohibited procedures are 1) Anabolic agents, 2) Peptide hormones, growth factors, related substances and mimetics, 3) β_2 agonists, 4) Hormone and metabolic modulators, 5) Diuretics and masking agents, 6) Manipulation of blood and blood components, 7) Chemical and physical manipulation, 8) Gene doping, 9) Narcotics and 10) stimulants.

The modern anti-doping control is based on segmentation of sports and focusing for a group of top-ranked athletes in individual sports, identified by an anti-doping organization, who are especially targeted for doping tests. This facilitates timely surprise tests outside competitions.

- Athletes obligated to provide whereabouts information
- In certain disciplines of team sports, first-tier team information is collected

Long-term routine monitoring of certain biological variables of an athlete will enhance the information of the changes of these variables for concluding a biological profile for each athlete as Passport. The values are not compared to population reference values but to an individual's personal reference values. Also the endocrinological passport and blood passport will be formed by these test results. This data will be an important tool in addition to traditional doping control. These values will also enhance and guide doping control already now and in future. Gene doping will be in future very difficult and challenging item for doping control. We will have only few tests for gene manipulation.

Drug poisoning – current hazards

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In Finland, the victims of fatal poisoning are usually found dead without any witnesses of the incident, and only roughly 6% of fatal poisonings take place after reaching any kind of medical care. In hospital, the mortality of poisoned patients is less than 1%. The drugs causing the most of acute fatal poisonings include opioids, antidepressants, antipsychotics, hypnotics and sedatives, adrenergic beta-blocking drugs, calcium antagonists, anticonvulsants, paracetamol and insulin. In this context, opioids are the most important class of poisons and the manner of death is usually accidental. Opioid induced respiratory depression is especially dangerous, if the person affected is asleep and unattended. In Finland, buprenorphine causes the most of fatal opioid poisonings, followed by tramadol, codeine, oxycodone, methadone and fentanyl. All of these substances are therapeutic drugs that are commonly diverted and abused. In case of buprenorphine, both smuggled mono-buprenorphine and buprenorphine – naloxone diverted from opioid maintenance treatment are involved. Buprenorphine fatalities are regularly associated with simultaneous use of sedatives, such as benzodiazepines, pregabalin or alcohol. Parenteral administration of the strong opioids is a major risk factor for poisoning, while poisonings due to the weak opioids are often suicides with massive oral overdoses. Concerning antidepressants, antipsychotics and many other medicines, there is a downward trend in fatal poisonings probably due to the improved safety of newer medicines. Among conventional illicit drugs, methamphetamine abuse has increased along with the more potent dextro-methamphetamine, possessing a higher abuse potential. The range of illicit drugs has recently exploded along with the emergence of new psychoactive substances (NPS). While many NPS proved to be transient on the illicit market, the stimulant alpha-pyrrolidinovalerophenone is more established. Until now, NPS have not been a major cause of poisoning. However, the recent appearance of new potent opioid derivatives, including U-47700, gives rise to serious concern.

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Responding to new psychoactive substances in the European Union: early warning, risk assessment and control measures

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New psychoactive substances make up a broad range of drugs — such as cannabinoids, opioids, stimulants, anxiolytics and sedative-hypnotics, dissociatives, and hallucinogens — that are not controlled under the 1961 and 1971 United Nations international drug control conventions but may pose comparable threats to health.

Over the last decade or so there has been an explosive growth in the number, type, and availability of new psychoactive substances on Europe's drug market. By the end of 2016, more than 620 new substances were being monitored — 70% of which appeared in the last five years. Many of these new substances are intended to be 'legal' replacements for controlled drugs such as cannabis, heroin, cocaine, amphetamines, MDMA, benzodiazepines, and LSD. They are sold as a range of branded and unbranded products including 'legal highs', 'research chemicals' and 'food supplements', or passed off as controlled drugs to unsuspecting users. As the range of substances and products has grown, consumer groups have also broadened out from small numbers of people who explore them for novel experiences and effects (often called 'psychonauts') and other 'early adopters' (such as electronic dance music fans), into wider groups of recreational users, people who self-medicate, people looking to improve their work performance or how they look, prisoners, as well as chronic and marginalised drug users. This has led to a range of challenges for public health policy and practice, including those related to the growing number of non-fatal and fatal poisonings.

In Europe a 3-step legal framework of early warning, risk assessment, and control measures allows the European Union to rapidly identify and react to public health threats caused by such substances. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is responsible for the first two steps in this system, namely operating an early warning system with Europol (the EU Police agency) and conducting risk assessments. While the European Commission, Parliament and Council of the European Union are responsible for control measures.

In this presentation we trace the development of this phenomenon; discuss the current situation in Europe from the perspective of the work of the EMCDDA; and, highlight some of the major concerns and challenges arising from this complex and serious public health problem using the fentanils — highly potent narcotic analgesics — as a case study. We conclude with some thoughts on what we may see next from this remarkable chemical health threat and some of the developments required for early warning and response in order to better protect public health.

New Psychoactive Substances (NPS) in Finland – challenges and legal responses

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NPS are substances that are not controlled by the UN conventions but are abused similarly. Over the last decade the number of NPS reported e.g. to the UNODC Early Warning Advisory system is already over 700. The diversity of NPS has increased and typical globally is also the diversity of regional patterns of their emergence. The emergence of NPS and the health harms relating to their use has challenged policy makers to respond to the issue. The traditional drug control regime proved too slow and various legislative responses have been taken, also in Finland.

The NPS market sourcing to Finland is primarily the internet (surface and deeb web). The substances are imported using regular mail or courier services and the new substances are in the first hand identified by the customs. There has been even more than 100 different substances identified annually. However, it is typical for NPS that only some of them stay on the market which is also confirmed by other indicators, such as police seizures, waste-water analyses and toxicological findings. Common to NPS is the lack of data and not only of their pharmacological and toxicological properties but even more so on the health harms associated with their use. This information is needed in addressing the possible emergency situations and also to support the informed scheduling decisions and control of the new substances as narcotics.

Since 2010 the Finnish legislation has evolved to meet these challenges. The availability of NPS is restricted by using a two tier scheduling system. The NPS can be scheduled as psychoactive substances banned from the consumer market or as narcotic substances. Legislation, however, is only one tool in addressing the potential health harms associated with the use of NPS.

Analyzing drugs of abuse in biological samples

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Testing drugs of abuse is an important tool in forensic toxicology and many other fields. The abuse of drugs is associated with numerous medical, social, and legal problems. Tests are performed e.g. to confirm an acute drug effect and monitor drug abstinence. The drugs with potential for abuse are mostly different psychoactive drugs including opioids, stimulants, sedatives/hypnotics and hallucinogens. In addition, the last decade has seen an increasing growth in numerous “designer drugs”. Depending on the purpose of testing, the substances of abuse may be determined from different biological samples. Various analytical methods including immunological assays and chromatographic/mass spectrometric methods have been used for detection of these drugs in biosamples. The tests can be divided into screening and confirmatory tests. Measurements can be either quantitative or qualitative in nature and they can be focused on only certain drugs or groups of drugs or they can be as coverable “generic” as possible. The aim and purpose of the testing in concern should be taken into account when selecting proper analytical methodology and strategy.

Absracts of posters

Evaluation of Aortic Valve Morphology in Hypercholesterolemic Mice by Magnetic Resonance Imaging

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Aims In aortic stenosis (AS), valvular calcification makes valves thicker and stiffen causing impairment of the valve function. The non-invasive cardiac magnetic resonance imaging (MRI) has been found potential in imaging AS but there is a room for improvement in the image resolution to be able to accurately detect composition and function of the valves. We used high-resolution cine-imaging to study changes in morphology of the aortic valves in a mouse model of AS.

Methods $LDLR^{-/-}ApoB^{100/100}$ mice were fed a high-fat diet (HFD) (42 % kcal from fat) or a normal chow diet (control) for 5 months. The mice heart were imaged at MRI and echocardiography, and the ejection fraction (EF), end diastolic and end systolic volumes were determined. MRI imaging was correlated with the histological staining: hematoxylin-eosin and Mac-3 for the macrophages.

Results From the MRI cine-images, the aortic wall and the atherosclerotic plaque were clearly separated and MRI demonstrated significant decline in EF (13%, $p<0.05$) in HFD mice compared to controls. Similarly, echocardiography revealed a marked reduction in EF (33%, $p<0.01$) in HFD mice compared to controls. The end systolic images of the aortic valves showed atheroma plaque and valve dysfunction. MRI and histological analysis revealed more severe atheromatous changes in the HFD mice compared to control (19%, $p<0.05$; 32%, $p<0.01$, respectively). In the histological analysis, area of aortic sinus was dilated 71% ($p<0.001$) and enlargement of area of aortic cusps (91%, $p<0.001$) was seen in HFD mice compared to controls.

Conclusions In hypercholesterolemic mice valvular atherosclerotic plaque and stenosis as well as reduction of EF was noted. Dysfunction and morphological changes of the aortic valves were clearly visualized by the cine MRI providing a non-invasive tool to monitor aortic valve morphology in mice.

Phencyclidine-induced changes in the metabolic activity of the rat brain

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Promising preclinical drug candidates often fail in the clinical phase and this has also been the case in development of novel drugs for schizophrenia. One key challenge in discovering novel drug candidates is to translate schizophrenia-like symptoms into appropriate preclinical models. Currently, the most commonly used approach is to induce schizophrenia-like symptoms with phencyclidine (PCP). However, there is a need to understand better the validity of this model.

Here our aim was to study the effects of acute and sub-chronic PCP exposure to the metabolic activity of the rat brain. Three treatment groups (N = 6 per group) were included in the study: A) saline control, B) acute PCP (3 mg/kg s.c. 2 hours before euthanasia) and C) sub-chronic PCP (3 mg/kg s.c. for 5 days, twice daily). Brain samples of frontal cortex, striatum and hippocampus were collected and analyzed by non-targeted metabolite profiling with LC-qTOF-MS system using hydrophilic interaction (HILIC) column.

PCP altered brain amino acid metabolism; e.g. aspartate levels were lower in PCP-treated animals than those in controls. Furthermore, also differences between acute and sub-chronic PCP exposure were observed; e.g. animals treated with sub-chronic PCP had lower glutathione disulfide levels than controls. These results may be associated with PCP-induced alterations in amino acid transporters and amino acid metabolizing enzymes, e.g. excitatory amino acid transporter 1 and d-amino acid oxidase. Previously abnormal function of these transporters and enzymes have been associated with schizophrenia in human studies.

In conclusion, PCP altered amino acid metabolism in the rat brain and the observed changes are similar to those previously observed in patients with schizophrenia. Therefore, the present study further supports the face validity of PCP in inducing schizophrenia-like symptoms in rodents.