



## 3<sup>rd</sup> N€uromed School (Tetouan, Morocco 2012)

### **The Neuroscience of addiction**

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Training of young researchers, PhD students in particular, is one of the main objectives of the N€uromed programme. It is through these programmes that young generations of scientists receive high quality, multidisciplinary and broad training in the field of Neurosciences. This field, more than any other scientific domain, requires knowledge from a variety of disciplines including biology, chemistry, physics, mathematics and of course informatics and computer sciences. It is only through the convergence of these multidisciplinary fields that we can understand how the brain functions in health and how various diseases affect its normal functioning.

Past editions of the N€uromed School have successively covered the important fields of ***“Neuroplasticity and neurorepair”*** (Alexandria Egypt, 2010), and ***“Metabolism, Energy and brain imaging”*** (Blida Algeria, 2011). This year’s edition is on the ***“Neuroscience of Addictions”***. This is an important issue for society, because humans have always struggled with addictions to mind-altering substances. Yet, only in the past few decades have neuroscientists begun to understand precisely how these substances affect the brain — and why they can quickly become a destructive and even deadly habit. Today, thanks to new advances in brain imaging and other technologies, as well as to the use of animal models, we know that addiction is a disease characterized by profound disruptions in particular brain circuits, namely those circuits involved in reward processing and learning. Important questions have been (and are still) addressed by researchers. For

example, how genetics and environmental factors, such as stress, contribute to the neural disruptions that increase the risk of addiction.

This N€uromed School will address all topics related to addiction, including:

- Current theories of addiction and recent advances in its understanding in relation to the reward system
- Stress in relation with drug dependence and withdrawal
- Drug abuse and its psychiatric and societal consequences
- Behavioral and effective therapies for treating drug abuse and addiction.

Thanks to the organizing committee, international experts in the field will contribute to this N€uromed School, by delivering courses and conferences on general background as well as on most recent discoveries. The selected students will also receive training on Behavioral analysis of drug dependence and withdrawal in animals, Neurocircuitry of Addiction and on more general issues such as how to prepare a CV and a cover letter.

On behalf of the N€uromed Consortium and the Local Organizing Committee, we would like to welcome the all the participants, and extend our sincere thanks to the speakers for their help on this endeavor of transfer of knowledge across the Mediterranean area.

Mohammed Errami

President of the Organizing Committee and National Coordinator of N€uromed in Morocco

Driss Boussaoud

N€uromed Coordinator

## **MOLECULAR MECHANISMS TO DRUGS ADDICTION**

**Soraya L. Vallés, Department of Physiology, School of Medicine, University of Valencia**

Drug addiction has afflicted mankind for centuries, yet the mechanisms by which particular drugs lead to addiction, and the genetic factors that make some individuals particularly vulnerable to addiction, have remained elusive. The search for a better understanding of the neurobiological mechanisms in normal conditions and underlying the addictive actions of drugs of abuse and of the genetic factors that contribute to addiction should be given a high priority, as this should result in crucial advances in our ability to treat and prevent drug addiction. Learning how brain works in normal conditions and also the effects and the type of neurotransmitters existing inside brain, can help the society to understand and prevent drug addiction. The brain is flexible and contacts between neurons are constantly being formed and broken. Drugs also cause this to happen. Addiction involves craving, increasing tolerance for a drug and withdrawal symptoms. Drugs also stimulate the reward centre and make you feel good. A craving for drugs arises when you remember those feelings and want to experience them again. Drug tolerance can develop in different ways. Changes may occur in your metabolism (your liver breaks down certain substances faster) or in your neurons themselves. If your body is constantly receiving drugs, that can inhibit the release of neurotransmitters. It can also reduce the number of nerve receptors. Then you need to take more drugs to achieve the original effect. If you stop taking a drug, and your body abruptly does not get the drugs it is accustomed to, your neurons do not immediately revert back to normal. The nerve receptors are now too few, the release of neurotransmitters is too low, or the MAOs have to work too hard. Your body has not yet adapted to the absence of drugs. This precipitates withdrawal symptoms. From the basic neuroscience perspective, study of the neurobiology of drug addiction offers a new opportunity to establish the biological basis of a complex and clinically relevant behavioural abnormality.

## **The last generation of designer drugs**

*Liana Fattore*

*CNR Neuroscience Institute-Cagliari, National Research Council-Italy*

Synthetic drugs are among the most commonly abused drugs in the world. Designer drugs are synthetic psychotropic drugs which belong to a group of legally or illegally produced substances that are structurally and pharmacologically very similar to common psychoactive drugs, and that typically exert stimulant, hallucinogenic, ecstasy-like or marijuana-like effects. In the past, designer drugs were often used during all-night dance parties, but in recent years they have become increasingly popular among recreational drug users, especially among young people. A new class of "designer drugs" has recently emerged on the drug use market, known as "legal highs" or "herbal highs", which are consumed in multiple settings from college bars to parks to private house parties. They include a wide range of products, from natural plant-originated substances to synthetic compounds that can be purchased both online and from high street retailers. Emergence, rapid dissemination and unpredictable effects of this new generation of designer drugs are challenging social and health professionals. Similarly, the manufacture and trafficking of these clandestinely produced drugs represent a serious problem for local authorities and law enforcement authorities worldwide. These psychoactive compounds are available via the Internet, frequently legal, and often perceived as safe by the public. Unfortunately, these drugs often have adverse effects, which range from minimal to life-threatening. While many of them remain unfamiliar to health care providers, the slow process of their classification facilitates their spreading, as once a certain substance receives an illegal drug classification, dealers and users usually move to another, slightly different molecule that is still legal. Clinicians and emergency medical staff must be familiar with these important new classes of drugs, and should maintain a high degree of alertness for their use and its possible psychiatric effects in vulnerable people. This talk will discuss the background, pharmacology, clinical effects, detection, and management of the most abused designer drugs, with particular emphasis on the very last, constantly changing, generation of designer drugs, i.e. that of synthetic cannabinoids or "Spice drugs".

## **ANIMAL MODELS OF ADDICTION**

**Paola Fadda**

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University of Cagliari, Cittadella Universitaria, Monserrato (Cagliari), Italy.

Drug addiction can be regarded as a behavioural syndrome characterised by compulsive drug taking and seeking behaviour with repeated relapse in drug use. Addictive behaviour may even recur again after many years of abstinence in spite of negative consequences for the individual, including death.

Addiction is a chronic condition and because of its unending nature, with relapses and remissions. Scientist now agree to define it as a “brain disease” comparable to other chronic diseases, such as diabetes and hypertension. Many factors contribute to drug addiction, and after repeated exposure complex changes develop in the brain, changes that are just now beginning to be elucidated.

Preclinical studies utilizing animal models have seriously contributed to progress in this area, and have provided a significant insight into the knowledge of the neuroanatomical circuitries, neurophysiological functions, neurochemical changes, and behavioral processes underlying addiction. The aim of this presentation is to critically review the most common behavioral animal models and tasks used by neuroscientists to study addiction and substance abuse. Advantages and limits of the drug discrimination procedure, the intracranial self-stimulation models, the conditioned place preference protocol, the acute and chronic drug self-administration procedures, and the extinction/reinstatement animal models will be discussed.

## **Atypical drug of abuse: caffeine properties and dependence**

Micaela Morelli, University of Cagliari, Dpt. of Biomedical Sciences, Cagliari, Italy

Caffeine, a natural xanthinic alkaloid, is one of the most popular psychostimulant substance consumed worldwide due to its ability in exerting psychostimulation of a mild extent usually devoid of severe unwanted effects.

Psychostimulation by caffeine includes increased wakefulness, delayed need for sleep, reduced fatigue perception, augmented alertness. Caffeine also elicits rewarding effects, associated with a beneficial influence on mood, and interferes with the perception of stimuli, bearing, in addition, discriminative properties towards other psychostimulants. Furthermore, nootropic properties have been suggested for caffeine based on its beneficial effects in tests measuring memory function. Interestingly, caffeine-mediated central effects may powerfully influence those of other centrally active substance. Several studies have shown, in fact, that caffeine may potentiate the motor stimulant effect of amphetamine and cocaine.

A wealth of experimental evidence indicates that the most commonly manifested biological effects of caffeine arise from its action on adenosine receptors primarily the A1 and A2A, although the participation of non-adenosinergic mechanisms in caffeine effects upon intake of high doses, may exist.

Although caffeine consumption is generally not associated with harmful consequences, moderation in caffeine intake is advisable to selected categories of individuals, such as persons particularly susceptible to its adverse effects. Importantly, the ability of caffeine in interfering with the effects of centrally active substances, including addictive psychostimulants, may represent a further risk factor associated with its consumption.

## **Stress responses underlying drug dependence and withdrawal**

**Angelo Contarino, University Bordeaux 2, France**

Drug dependence and withdrawal are usually associated with deregulated stress responses that might contribute to the establishment and maintenance of the disease. In this talk, I will present some studies from our laboratory showing that stress-responsive systems, such as the corticotropin-releasing factor (CRF), the dynorphin/kappa opioid receptor (KOR) and the norepinephrine systems differentially contribute to the myriad of somatic and emotional signs and symptoms of drug dependence and withdrawal. In particular, using clinically-relevant experimental mouse models, our work demonstrates a critical, but differential, role for each of the two known CRF receptor pathways, CRF<sub>1</sub> and CRF<sub>2</sub>, in drug dependence and withdrawal. Indeed, genetic inactivation of CRF<sub>1</sub> receptors eliminates dysphoria-like states but dramatically worsen the somatic signs and the ability to cope with the stress of opiate withdrawal (*PNAS*, 2005; *Neuron* 2007). In contrast, genetic inactivation of CRF<sub>2</sub> receptors eliminates dysphoria-like, anhedonia-like and somatic signs of opiate withdrawal without impairing stress coping (*Neuropsychopharmacology* 2008; *Molecular Psychiatry* 2011). Furthermore, our studies reveal brain region-specific changes in CRF, dynorphin and norepinephrine systems, indicating dissociation between brain stress-responsive systems underlying drug dependence and stress-coping abilities. These findings suggest new strategies for treating drug dependence and withdrawal without impairing stress-coping ability.

# **Role of the endogenous cannabinoid system in reward processes**

**Marcello Solinas**

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Drugs and natural rewards are believed to activate common brain circuits that evolved in mammals to favour fitness and survival. For decades, endogenous dopaminergic and opioid systems have been considered the most important systems in mediating brain reward processes. Over the last several decades, an endogenous system comprised of cannabinoid receptors, endogenous ligands for these receptors and enzymes responsible for the synthesis and degradation of these endogenous cannabinoid ligands has been discovered and partly characterized. Experimental findings strongly suggest a major involvement of the endocannabinoid system in general brain reward functions. First, cannabinoid receptors are found in brain areas involved in reward processes, such as the dopaminergic mesolimbic system. Second, natural and synthetic cannabinoids and endocannabinoids can produce rewarding effects in humans and laboratory animals. Third, activation or blockade of the endogenous cannabinoid system has been shown to modulate drug and natural rewards. Fourth, abused drugs and natural rewards have been shown to alter brain levels of endocannabinoids in the brain. Altogether, this evidence demonstrates that the endocannabinoid system plays a key role in brain reward processes. Therefore, this system may be targeted for the development of new drugs for treatment of psychiatric disorders involving malfunctioning of the reward system.

## REFERENCES

Fernández-Ruiz J, Hernández M, Ramos JA. *Cannabinoid-dopamine interaction in the pathophysiology and treatment of CNS disorders*. *CNS Neurosci Ther*. 2010 Jun;16(3):e72-91. Epub 2010 Apr 12. Review.

Solinas M, Goldberg SR, Piomelli D. *The endocannabinoid system in brain reward processes*. *Br J Pharmacol*. 2008 May;154(2):369-83. Epub 2008 Apr 14. Review.

Maldonado R, Valverde O, Berrendero F. *Involvement of the endocannabinoid system in drug addiction*. *Trends Neurosci*. 2006 Apr;29(4):225-32. Epub 2006 Feb 17. Review.

## **MARIHUANA AND ALCOHOL ADDICTION: TEENAGER'S PROBLEM**

**Soraya L. Vallés**

**Department of Physiology, School of Medicine, University of Valencia**

The term drug is used to refer to substances that cause an altered state of mind and are capable of producing addiction. This term includes not only substances which are popularly thought of as drugs by their illegal status, but also various psychotropic drugs and legal substances used as snuff, alcohol or xanthine-containing beverages such as coffee, in addition to household chemicals or work as adhesives, glues, and volatile solvents. Drugs are not in themselves positive or negative. Meaning that for a specific person and their social environment are the effects of a substance, which their consumption may depend on end up being problematic. Marijuana is the most commonly used illegal drug in Europe and 42 percent of high school seniors reported having tried marijuana. About 5 percent said they had used it daily during the previous month. Also if teenagers consume marijuana also consume alcohol. About 60 percent of the likelihood of becoming a heavy drinker, a frequent marijuana user or of becoming dependent on marijuana can be attributed to genes, while about half of the likelihood of being an alcoholic can be traced to genetics. The genes that make people susceptible to alcoholism also make them prone to becoming addicted to marijuana. Marijuana's active ingredient, THC, acts on the brain's cannabinoid system, which is involved in learning, memory, appetite and pain perception. On the other hand, medical uses for marijuana including alleviating pain and boosting appetite in people with cancer and other serious illnesses. When teenagers smoke cannabis and drink alcohol at the same time they can experience nausea and/or vomiting or they can react with panic, anxiety or paranoia. Mixing cannabis with alcohol can increase the risk of vulnerable people experiencing psychotic symptoms. In the past, researchers have often studied the addictive properties of drugs such as tobacco, cocaine, marijuana, heroin and alcohol separately. But different studies indicate that drugs may be study in the future as substance abuse together.

## **Clinical and psychopathological aspects of addiction, Mohamed Agoub**

### **Psychiatric Comorbidity of addiction, Meryem Elyazaji**

Centre Psychiatrique Universitaire Ibn Rochd , Faculté de Médecine et de Pharmacie de Casablanca, Morocco

Comorbidity between addiction and psychiatric disorders is very common. It reflects both a high risk for addiction in patients with mental disorders and a high occurrence of psychopathology triggered by substance use. However, the meaning of the comorbidity addiction-mental disorders concerning the mechanisms underlying psychopathology and substance use, the influence of addiction on the course of mental disorders and the influence of mental disorders on the course of substance use, and the implications for management of both disorders are still unclear and not entirely understood.

For example, the high rate of comorbidity between schizophrenia and substance use is likely to reflect common contributing factors and brain substrates. The involvement of brain dopaminergic pathways is likely to be a shared feature in this comorbidity, and is associated with poorer clinical outcomes and contributes significantly to their morbidity and mortality.

## **Circadian neurobiology of drug addiction**

**Jorge MENDOZA**

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Drug addiction is a brain pathology which affects millions of people in the world. Interestingly, both drugs of abuse and the consumption of highly palatable diets converge on a shared pathway within the brain to modulate behaviour. Recent studies have shown that main suprachiasmatic clock (SCN), which controls almost all circadian rhythms, may modulate drug and highly palatable food intake, suggesting a link between the circadian system and the brain circuitry underlying reward. Circadian cycles in SCN neurons revolve around transcriptional/posttranslational feedback loops encoded by a series of clock genes (*Clock*, *Bmal1*, *Per* and *Cry*). Drugs of abuse as cocaine induce the expression of clock genes in different brain areas in a rhythmic manner. Furthermore, there is an involvement of several clock genes in the development of drug-induced behaviours. The role of the circadian clock(s) and genes on the regulation of neurobehavioural disorders of drug abuse or compulsive food intake is not totally known. The understanding of the functional crosstalk between the circadian and the central reward systems may yield important new insights into the cause and treatment of drug addiction or compulsive eating disorders.

### **References**

1. Abarca C, Albrecht, U., Spanagel R (2002) Cocaine sensitization and reward are under the influence of circadian genes and rhythm. *Proc Natl Acad Sci USA* 99(13): 9026-9030.
2. Hastings MH, Reddy AB, and Maywood ES (2003) A clockwork web: circadian timing in brain and periphery, in health and disease. *Nat Rev Neurosci* 4: 649-661.
3. McClung CA, Sidiropoulou K, Vitaterna M, Takahashi JS, White FJ, Cooper DC, Nestler EJ (2005) Regulation of dopaminergic transmission and cocaine reward by the *Clock* gene. *Proc Natl Acad Sci USA* 102(26):9377-9381.
4. Mendoza J, Challet E (2009) Brain clocks: from the suprachiasmatic nuclei to a cerebral network. *Neuroscientist* 15(5): 477-488.
5. Takahashi JS, Hong HK, Ko CH, McDearmon EL (2008) The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet.* 9(10): 764-775.

## **Toxicity associated to the abuse of amphetamine-related drugs**

Micaela Morelli, University of Cagliari, Dpt. of Biomedical Sciences, Cagliari, Italy

Amphetamine and its derivatives exhibit psychostimulant and rewarding properties but can also induce neurochemical toxic effects. MDMA (N-methyl-3,4-methylenedioxy-amphetamine), known as ecstasy, is the most popular amphetamine derivative and may induce death caused by hyperthermia, hyponatremia and cardiovascular adverse effects. Moreover, use of MDMA may disrupt brain functions like attention, memory and mood.

Specific neurotoxic damage by MDMA to 5-hydroxytryptamine and dopaminergic nerve endings in rodents and in primates has been demonstrated both biochemically and histochemically. These neurotoxic effects appear to result from free radical formation which in turn induces oxidative stress and from hyperthermia. Evidence for the occurrence of MDMA-induced neurotoxic damage in human users, however, remains ambiguous since such evidence is complicated by the fact that many users often take other substances concomitantly, either intentionally or due to impurities in ecstasy tablets. Several findings have suggested that neuroinflammation may play an active role in the pathogenesis of neurodegenerative diseases and microglia and astroglia activation appear to have an important role in neurotoxicity. Therefore MDMA-induced microglia and astroglia activation appear particularly relevant for MDMA-associated toxicity since they may generate several reactive species (e.g., nitric oxide, superoxide, cytokines) favouring neurodegeneration.

# **Disruptions of hypothalamic neuropeptidergic systems in eating disorders**

## **Anorexia nervosa and Bulimia**

**Nicolas Chartrel**

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Anorexia nervosa and bulimia are eating disorders that are now considered as addictive behaviors, and close neuronal interactions have been found between the dopaminergic reward system and the hypothalamic nuclei that control feeding behavior.

During this presentation, we give a brief overview of our current knowledge on the disruption of various hormonal and neuropeptidergic systems in two eating disorders, i.e. anorexia nervosa and bulimia. More specifically, five distinct groups of patients are described i.e. healthy patients (C), restrictive anorectic patients (AN), anorectic patients with binge-eating purging episodes (AN-BP), constitutionally thin patients (CT) that are severely underweight women but with no abnormal feeding behavior, and bulimic patients (BN).

The two anorexigenic peptides leptin and PYY, and the two orexigenic neuropeptides ghrelin and 26RFa have been studied. In AN patients, circadian plasma leptin and PYY levels are drastically decreased. In contrast, daily circulating levels of the two orexigenic neuropeptides ghrelin and 26RFa are strongly increased in AN patients. In CT women, that have an equilibrated energy balance, plasma levels of the four regulating peptides are not significantly different from the circulating levels observed in C patients.

Binge-eating purging episodes in C or AN patients do not influence the plasma levels of leptin and 26RFa. In contrast, circulating ghrelin and PYY levels are dramatically decreased in BN and AN-BP women.

In conclusion, AN patients show an orexigenic profile of hormones regulating appetite that reflects a normal adaptive mechanism of the organism to promote energy intake and to increase fat stores in response to undernutrition. In patients that display binge-eating episodes, long-term regulating hormones (leptin and 26RFa) are not altered. In contrast, short-term regulating peptides are drastically decreased and thus may promote bulimic episodes by disrupting the regulation of circadian food intake.