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METAPLASTICITY IN THE VENTRAL TEGMENTAL AREA PROMOTES ALCOHOL- AND PYCHOSTIMULANT-INDUCED CONTEXTUAL LEARNING

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Addiction involves a maladaptive form of learning and memory in which drug-related experiences are remembered powerfully, resulting in persistent and uncontrollable drug seeking. Synaptic plasticity in the mesolimbic dopaminergic system originating in the ventral tegmental area (VTA) is critically involved in the learning of information related to rewards, including drugs of abuse such as alcohol and psychostimulants. Previous life experiences can alter the capacity of synapses to undergo activity-dependent plasticity in the CNS. This 'plasticity of synaptic plasticity', termed metaplasticity, may affect the future learning capacity of animals. NMDA receptor (NMDAR)-mediated glutamatergic transmission onto dopamine neurons undergoes long-term potentiation (LTP) following repeated pairing of glutamatergic input stimulation with postsynaptic burst firing. Induction of this form of plasticity requires amplification of spike-evoked Ca^{2+} signals by preceding synaptic activation of metabotropic glutamate receptors (mGluRs) coupled to the generation of inositol 1,4,5-trisphosphate (IP_3). Our recent studies indicate that repeated *in vivo* exposure to ethanol (2 g/kg, i.p. three times daily for 7 d) or amphetamine (5 mg/kg, i.p., once daily for 3-7 d) causes increased susceptibility to the induction of NMDAR LTP in VTA dopamine neurons. Enhancement of NMDAR plasticity results from an increase in mGluR/IP3 signaling, which occurs through a protein kinase A (PKA)-dependent mechanism. We have further found that prolonged social isolation (>3 weeks) from postnatal day 21 (P21), but not from P42, leads to a similar enhancement of NMDAR plasticity. Long-term social isolation occludes the effect of subsequent amphetamine exposure on mGluR/IP_3 signaling, suggesting the involvement of a common adaptive mechanism involving PKA. Repeated ethanol exposure or long-term social isolation facilitates the learning of cocaine-, amphetamine-, or ethanol-associated contextual stimuli assessed using a conditioned place preference (CPP) paradigm. Finally, acquisition of amphetamine CPP is attenuated by intra-VTA infusion of a PKA inhibitor. These data suggest that PKA-dependent regulation of IP3 signaling in the VTA, which gates the 'inducibility' of NMDAR plasticity, may represent a common neural substrate by which various life experiences influence the capacity of animals to form drug-associated memories.

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EXCESSIVE ETHANOL CONSUMPTION DISRUPTS BDNF-MEDIATED CONTROL OF ETHANOL DRINKING BEHAVIORS - A ROLE FOR THE p75-NTR RECEPTOR

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The brain-derived neurotrophic factor (BDNF) plays an important role in synaptic plasticity, as well as learning and memory. BDNF has also been implicated in psychiatric disorders including drug addiction. We previously showed that the BDNF pathway plays a protective role against the development of alcohol (ethanol) abuse disorders. Specifically, we found that voluntary moderate intake of ethanol results in an increase in the expression of BDNF in the dorsal striatum, and specifically in the dorsolateral striatum (DLS) of mice and rats [1-3]. We further showed that the activation of the BDNF receptor tyrosine kinase, TrkB in the DLS of rats reduces rat operant self-administration of moderate amount (10%) of ethanol [2]. Conversely, infection of DLS neurons with a virus expressing siRNA-against the BDNF gene increased operant responding for a 10% ethanol solution. Next, we determined the expression levels and function of BDNF in rodents voluntarily consuming excessive (20%) intake of ethanol. We observed a breakdown in the corticostriatal levels of BDNF. Specifically, excessive ethanol intake did not alter the levels of BDNF in the dorsal striatum [3], and a marked decrease of BDNF mRNA was observed in the medial prefrontal cortex (mPFC). Furthermore, knockdown of BDNF levels or activation of the BDNF pathway in the DLS does not alter ethanol operant self-administration in rats with a history of excessive (20%) ethanol intake. Activation of the BDNF receptor, p75-NTR, produces responses that are opposite to those of TrkB. We therefore hypothesized that a history of excessive drinking alters p75-NTR expression and/or neuronal localization. We found that excessive ethanol drinking leads to alterations in the synaptic localization of p75-NTR, suggesting that changes in the membranal composition of the BDNF receptor in the DLS contribute to the development of excessive drinking behavior. Together, our results suggest that a history of excessive consumption of ethanol leads to a breakdown in the BDNF-mediated homeostatic pathway, which in turn contribute to the transition from moderate to uncontrolled ethanol intake.

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Non Invasive Screening for Liver Cirrhosis in Addicted Patients

Organizer/Chair: Sebastian MUELLER / Co-Chair: Laurent SANDRIN

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IS LIVER STIFFNESS THE NOVEL GOLD STANDARD PARAMETER TO DIAGNOSE ALCOHOLIC LIVER CIRRHOSIS?

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Noninvasive screening for liver cirrhosis in patients addicted to drugs or alcohol has been a continuing problem in internal and addictive medicine. This has dramatically changed with the recent introduction of transient elastography (Fibroscan) to directly measure liver stiffness (LS). This novel technique is expanding rapidly around the globe since it allows the diagnosis of liver cirrhosis in a true bed-side manner within minutes.
LS is an excellent screening parameter for cirrhosis with a high negative predictive value. Thus, a normal LS < 6 kPa excludes ongoing liver disease while a LS of 8 kPa and 12.5 kPa represent generally accepted cut-off values for F3 and F4 fibrosis. Meanwhile, LS has also been successfully used to monitor treatment outcome of patients with alcoholic liver cirrhosis and as prognostic parameter for hepatic complications such as the risk of variceal bleeding or hepatocellular carcinoma.
However, it is important to conceive that several other factors apart from cirrhosis stage may affect LS. Such factors include liver inflammation, liver congestion, cholestasis and rare conditions such as amyloidosis or mastocytosis. Thus, although LS is an excellent screening tool for liver disease, it should always be interpreted in the clinical context. For such a hepatological expert interpretation of LS values, a concomitant ultrasound and laboratory parameters are required which will increase the diagnostic accuracy over 99%. Novel actual algorithms will be discussed especially with regard to alcoholic liver disease, how to interpret increased LS values within the clinical setting.

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SERUM OSTEOPONTIN LEVELS AS A DIAGNOSTIC MARKER FOR HEPATIC FIBROSIS

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Background and Aims: Osteopontin (OPN) is a multifunctional matricellular protein that plays a significant role in innate immunity, cell survival, tumor invasion, and angiogenesis. In the present investigation we have measured serum OPN levels in progressive fibrosis and liver cirrhosis and the data are correlated with hepatic expression of OPN.
Methods: Patients with hepatic fibrosis were scored as thin fibers in the periportal (F1), many thick fibers in the periportal to midzonal areas of the lobules (F2), bridging fibrosis (F3) and liver cirrhosis (F4) by an experienced hepatopathologist. Serum samples were obtained from each group. Serum OPN levels were measured using enzyme linked immunosorbent assay (ELISA) using recombinant human OPN as standard. Immunohistochemical staining for OPN was carried out in the hepatic tissue obtained through liver biopsy and the staining intensity was correlated with serum OPN levels.
Results: In order to employ serum OPN as a progressive marker for hepatic fibrosis and liver cirrhosis, we measured serum OPN levels and correlated with hepatic OPN expression. Serum OPN levels were significantly increased from periportal fibrosis (F1) to liver cirrhosis in a progressive manner. The data were highly correlated with the staining intensity of hepatic OPN expression.
Conclusions: The results indicate that serum OPN levels reflect the degree of hepatic fibrosis and could be used as a prognostic marker towards progression of hepatic fibrosis to liver cirrhosis.