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PLENARY

IS MORE NEUROGENESIS BETTER?

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Adult hippocampal neurogenesis is a unique form of plasticity that generates new neurons in the dentate gyrus throughout life. Adult-born neurons have been implicated in both cognitive functions and in mediating the behavioral effects of antidepressants. However, it is not known whether stimulation of adult hippocampal neurogenesis is sufficient to improve cognition and mood. We used an inducible genetic gain-of-function strategy to cell autonomously augment adult neurogenesis. We show that mice in which the pro-apoptotic gene, Bax, is deleted specifically in adult progenitors have increased survival of adult-born dentate granule neurons, exhibit enhanced neurogenesis-dependent synaptic plasticity and discriminate between similar contexts more efficiently than controls. In contrast, increasing the number of adult-born neurons did not produce an antidepressant-like behavioral response. Our findings suggest therefore that strategies designed to specifically stimulate adult hippocampal neurogenesis are likely to have pro-cognitive effects associated with improved pattern separation, but may not be sufficient to enhance mood.

SYMPOSIUM 1

SPATIAL LEARNING: A SCULPTOR OF NEO-NETWORKS

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During embryonic development, neuronal activity sculpts neuronal networks. Indeed, after an initial overproduction of neurons and contacts, regressive events will stabilize a particular set of contacts among many, thereby sculpting the precise circuits that are crucial for a given function. We will show that similarly to this selective stabilization process, adult neuronal networks are sculpted during learning. Indeed, the adult dentate gyrus has the peculiarity to produce new neurones throughout the life of an individual. This region is crucially involved in memory and increasing evidence suggests that the addition of adult-born neurons contribute to memory processes. We will show that spatial learning regulates homeostatically the number of new neurons and shapes the dendritic arbor of the set of new neurons stabilized by learning. This 'epigenetic' specification of neo-neonetworks are long lasting, depend upon the level of cognitive demand and NMDA receptors. Altogether, these results showed that in addition to remodelling pre-exiting networks, learning sculpts novel networks. In the search for the structural changes underlying long-term memory, these findings highlight that shaping neo-networks is important in forming spatial memories.

MOLECULAR MECHANISMS UNDERLYING NEUROGENESIS

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Neural stem cells (NSCs) generate new neurons throughout life in two distinct areas of the mammalian brain: the subventricular zone (SVZ) lining the lateral ventricles and the hippocampal dentate gyrus (DG). How gene expression signatures differ among NSCs and immature neurons within and between the adult neurogenic regions is unknown. We used transgenic mice expressing fluorescent reporters to isolate NSCs and their progeny directly from the adult brain. Comparison of the transcriptomes of these distinct cell populations derived from both neurogenic areas revealed that NSCs from the adult DG and SVZ are highly similar but that gene expression profiles substantially diverge in immature neurons, suggesting that neuronal specification occurs at the stage of DCX expression. We provide evidence for the functional significance of several pathways newly identified by transcriptome analyses. Thus, the data provided here establish a gene expression-based framework to understand the molecular mechanisms of neurogenesis and stem cell diversity in the adult brain.

THE CONTROL OF NEUROGENESIS IN THE OLFACTORY BULBS

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In mammals, new neurons are continuously recruited into the olfactory bulb throughout life. Most of the adult-generated neurons, granule and periglomerular cells, originate from the subventricular zone lining the lateral ventricles and migrate via the rostral migration stream towards the bulb. Although thousands neurons arrive to the bulb per day, the function of this never-ending integration of new neurons remains highly debated. This ongoing neurogenesis is tighly regulated by sensory experience and is essential for the maintenance of the olfactory bulb network. Behavioral explorations of different models where neurogenesis was manipulated indicated that bulbar neurogenesis is necessary for some, but not all, olfactory functions. Adult olfactory bulb neurogenesis seem not to be involved in perception *per se*, but rather in cognitive function. Adult-generated olfactory bulb neurons are required for olfactory fear conditioning, olfactory perceptual learning and odor memory, suggesting that bulbar neurogenesis provides unique functions for olfaction.

EXPERIENCE-DEPENDENT FUNCTIONAL INTEGRATION OF NEW NEURONS IN ADULT DENTATE GYRUS

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New neurons are continuously integrated into existing neural circuits in adult dentate gyrus of the mammalian brain. Accumulating evidence indicates that these new neurons are involved in learning and memory,

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although it is not clear how these small numbers of new neurons support memory functions. Using a retrovirus-mediated single-cell knockout technique, we have demonstrated that the survival of new neurons early after their birth is dependent on their own NMDA receptor, indicating that input activity onto the new neurons may determine new circuits formed by new neurons through selective neuronal survival/death. Further using an immediate early gene activity-mapping method, we have showed that functional integration of new neurons is determined by animal's experience during a similar early time period. These findings cooperatively indicate a unique mechanism of young new neurons during a critical period, in which experience determines circuits formed by new neurons through the selective neuronal survival/death, resulting in a functional change in the dentate gyrus that may mediate learning and memory.

SYMPOSIUM 2

ANTIDEPRESSANTS AND TURNOVER OF NEURONS AND SYNAPSES

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Antidepressant treatments have been shown to promote different forms of neuronal plasticity, including neurogenesis, synaptogenesis and neuronal maturation in the hippocampus. At least some of these plastic effects are mediated by brain-derived neurotrophic factor (BDNF). Antidepressants increase BDNF synthesis and signaling in the rodent hippocampus and cortex, and this signaling is required for the behavioral effects of antidepressant drugs. We have found that BDNF signaling does not appear to be required for the antidepressant-increased increase in neuronal precursor proliferation, but the survival of the newborn neurons is compromised when BDNF signaling is disturbed. Furthermore, we found that antidepressant increase the turnover of new neurons rather than just neurogenesis in hippocampus. However, it is not known how antidepressant treatments influence the structure and function of neuronal networks in brain. We have recently shown, in collaboration with Dr Maffei's lab, that chronic antidepressant treatment reactivates critical period-like plasticity in the visual cortex adult rats. Furthermore, we found that the impaired vision brought about by a closure of one eye throughout development was rescued in adult rats if adult antidepressant treatment was combined with the opening of the weak eye and patching of the better eye in rats in adulthood. These effects were associated with increased BDNF and cold be inhibited by blocking BDNF signaling through TrkB receptors, emphasizing the important role of BDNF in adult plasticity. Our data suggest that antidepressant treatment, by increasing neuronal and synaptic turnover and reactivating developmental-type cortical plasticity, can help to repair malfunctioning neuronal networks brought about by imbalanced early experiences, when antidepressant treatment is combined with environmental rehabilitation. This hypothesis suggests a completely novel mechanism for the action of antidepressant drugs where the drug acts permissively to facilitate the effects of rehabilitation of the structure of neuronal networks in brain.

IL1, VEGF, ANTIDEPRESSANTS AND NEUROGENESIS

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In addition to neurochemical imbalances contributing to major depressive disorder (MDD), there is now strong evidence of structural alterations in the brains of MDD patients. Brain imaging studies have reported a decrease in the volume of key brain regions implicated in MDD, including the hippocampus and prefrontal cortex, that could contribute, either directly or indirectly, to the core symptoms of depression, including decreased cognition, mood, motivation and reward. Studies of rodent models have also been informative, and demonstrate that exposure to stress decreases proliferation of neurons and/or glia, and decreases neurotrophic factor expression. In contrast, chronic antidepressant treatment (ADT) blocks the effects of stress, increases neuronal/glial proliferation, and increases neurotrophic factor expression. In particular, there is strong evidence for the role of brain derived neurotrophic factor (BDNF) and more recently vascular endothelial growth factor (VEGF) and interleukin 1 beta (IL-1beta) in the neurogenic effects of stress and antidepressants. We have found that chronic antidepressant treatment increases the expression of VEGF in the hippocampus, and that VEGF signaling in this region is required for neurogenic (specifically, increased proliferation) and the behavioral actions of ADT. We have also found that VEGF receptor 2 (VEGF-R2 or Flk1) is expressed on neuronal progenitor cells and underlies the induction of cell proliferation by ADT. In contrast, IL-1beta is involved in the neurogenic effects of stress and blockade of IL-1beta receptor attenuates the stress-induced decreased in cell proliferation in the hippocampus. These findings may lead to novel treatment strategies, including neurotrophic/growth factor signaling and neuronal proliferation to take advantage of these advances in our understanding of the neurobiology and treatment of depression.

THE CONTRIBUTION OF HIPPOCAMPAL NEUROGENESIS IN STRESS SYSTEM REGULATION: AN EXPLANATION FOR ITS INVOLVEMENT IN ANTIDEPRESSANT EFFECTS

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Stress exposures are high prevalent events which can cause dramatic outcomes on welfare, health and life span. Particularly, chronic stress can trigger anxiety/depression-related disorders which are one of the most leading causes of disability and health problem worldwide. Moreover, a large part of patients remains insensitive to current pharmacotherapy and exhibits high relapse rate. Hence, the uncovering of the relevant neurobiological processes involved in these disorders is of crucial importance for the development of better treatments. Recent researches suggest an involvement of hippocampal neurogenesis in behavioral effects of antidepressants (ADs) but the precise mechanisms through which new granule neurons can underlie antidepressant response remains poorly understood. We used the Unpredictable Chronic Mild Stress in mouse to investigate causality between changes in hippocampal neurogenesis and effects of both chronic stress and chronic ADs. While hippocampal neurogenesis ablation did not induce any depressive-like states or make mice more vulnerable to chronic stress, it prevented recovery following monoaminergic AD treatment, like imipramine and fluoxetine. On the contrary, the effects of CRF1 and V1b antagonists were not blocked by neurogenesis ablation suggesting that new hippocampal neurons could be used by ADs to restore stress system functioning. Indeed, we also demonstrated that this form of stress reduces hippocampal neurogenesis and severely impairs the relationship between hippocampus and stress hormone system: such as reactivity of dentate neurons to glucocorticoid stimulation, of downstream brain areas regulating HPA axis and the negative feedback on HPA axis. Finally, we revealed that fluoxetine can restore the ability of hippocampus to inhibit stress system only when neurogenesis is effective and can be stimulated. In summary, our experiments do not identify hippocampal neurogenesis changes as an etiological factor for stress-related disorders but indicate that ADs can act through adult-generated neurons to restore hippocampal control on stress systems, then enabling to initiate recovery.

SYMPOSIUM 3

REGULATION OF THE DEVELOPMENT OF DENTATE GRANULE NEURONS BY DISRUPTED-IN-SCHIZOPHRENIA 1 (DISC1)

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A balanced translocation of Disrupted in schizophrenia 1 (DISC1) gene was initially identified in a Scottish family with schizophrenia and other major mental disorders. DISC1 encodes a scaffold protein that is involved in the regulation of multiple processes of neurodevelopment both in early and adult neurogenesis. The signaling mechanisms of how DISC1 regulates neural development are still largely unknown. We have recently shown that, during adult neurogenesis, knockdown of DISC1 leads to enlarged cell body, accelerated morphogenesis and maturation of newborn granule neurons in the dendate gyrus of hippocampus, and these actions of DISC1 is mainly mediated through AKT/mTOR pathway. I will discuss our recent work on the further understanding of DISC1 function and signaling mechanisms in the regulation of neural development in early postnatal and adult brain.

ADULT NEUROGENESIS IN MICE AND MEN: POSSIBLE RELEVANCE FOR AGE-RELATED MEMORY IMPAIRMENT AND FOR PSYCHIATRIC DISORDERS SUCH AS SCHIZOPHRENIA

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The phenomenon of adult neurogenesis (aN), i.e. the generation of new functional neurons in the adult dentate gyrus of the hippocampus, has gathered much attention in the recent years, especially since it has been shown that this process takes also place in the human brain. A large number of variables regulate aN such as learning, exercise, stress, and age. Several lines of evidence based on the structure-function relationships support the involvement of neurogenesis in memory processing in the adult brain. In particular, adult-born hippocampal neurons have been shown to be related to complex forms of spatial or associative memories. One of the most interesting question deals with the possible relation of the age-related decline in neurogenesis and age-dependent memory impairment. Another important question deals with the role of aN in the pathophyisology of psychiatric disorders. Although a plethora of animal studies indicate an involvement of aN in the pathophysiology of depression and that stimulation of aN is essential for the mechanism of action of anti-depressant therapies, this view has recently kindled considerable controversy. Appropriate studies in humans failed to confirm a role of reduced hippocampal neural stem cell proliferation in depression, but suggest a contribution to the pathophysiology of schizophrenia. Disturbed aN may cause erroneous temporal encoding of new memory traces, thereby contributing to cognitive deficits observed in schizophrenic patients. This aN-hypothesis of schizophrenia is supported by neuroimaging as well as by several animal models. But to date it is completely unclear whether our basic knowledge of new neurons in the adult hippocampus might eventually help fight or even prevent mental illness.

ANTIPSYCHOTICS AND ADULT NEUROGENESIS

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Hippocampal dysfunction and/or atrophy are implicated in major neuropsychiatric disorders such as schizophrenia and mood disorders. It was postulated that some therapeutic properties of antidepressants, mood stabilizers and antipsychotics may arise from their ability to increase hippocampal neurogenesis, which, in turn, subsequently improves hippocampal function. However, the extent to which antipsychotics can modulate cell division and survival of newly generated cells within the hippocampus has been controversial. We examined the effects of chronic antipsychotic treatment on BDNF expression and on cell proliferation and survival in the adult rat hippocampus in normal rats and in rats with neonatal hippocampal lesion used as a model of schizophrenia. Haloperidol (0.05 and 2 mg/kg), clozapine (0.5 and 20 mg/kg), or vehicle were administered i.p. for 28 days followed by BrdU (200 mg/kg, i.p.). One group of rats was killed 24 h following BrdU administration and BrdU positive cells were quantified to assess the effects of drug treatment on cell proliferation. The remaining animals continued on antipsychotic medication for an additional three weeks following BrdU administration to assess the effects of antipsychotics on cell survival. Our results show that BDNF was decreased after antipsychotics in rats, in neonatally lesioned animals and in the human postmortem hippocampus. Twenty-four hours following BrdU, a low dose of clozapine (0.5 mg/kg) increased the number of BrdU-positive cells in the dentate gyrus (DG) by two-fold. Neither 20 mg/kg of clozapine or haloperidol had any effect on cell proliferation in DG. Moreover, neither drug at either dose had an effect on the number of newly generated neurons surviving in the DG three weeks following BrdU administration. These findings suggest that clozapine may influence the number of cells which divide, but antipsychotics do not promote the survival of the newly generated neurons at three weeks after a BrdU injection.

SYMPOSIUM 4

ADULT HIPPOCAMPAL NEUROGENESIS: IMPLICATIONS FOR ADDICTION

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Compulsive use of drugs of abuse, such as opiates and psychostimulants, is widely recognized as a disease of the brain, albeit one compounded by myriad genetic and social factors. While the primary target of addiction-related research efforts has been the 'reward' circuitry, e.g. dopaminergic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, the hippocampus is receiving increasingly more attention for its potential role in addiction. This is perhaps not surprising given that the hippocampus is anatomically positioned to influence brain reward circuitry and is altered both structurally and functionally after drug exposure. Further, the hippocampus appears to play a role in mediating the acute reinforcing properties of drugs of abuse, forming drug/context associations, and contribute to relapse to drug seeking after abstinence. Work suggests that postnatal experience can alter susceptibility to addiction later in life, and notably, the dentate gyrus of the hippocampus is primarily formed during this postnatal window. Therefore it is compelling that exposure to a wide variety of drugs of abuse can regulate the birth, differentiation and/or survival of new dentate gyrus hippocampal neurons in the postnatal brain. Here we review the work by the Eisch Laboratory and others on the proliferation, differentiation, and survival of postnatally-generated neurons in the hippocampal dentate gyrus of drug-naïve and drug-exposed animals, and our recent work on the molecular (e.g. Cdk5, Notch1) and microenvironmental (e.g. cytokines, vasculature) basis for postnatal neurogenesis and its alterations after drug exposure (e.g. cocaine, methylphenidate, opiates). We will highlight our recent data showing that reduced hippocampal neurogenesis enhances vulnerability in an animal model of cocaine addiction. Our recent work identifies reduced adult hippocampal neurogenesis as a

novel risk factor for addiction-related behaviors, and suggests that therapeutics to specifically increase or stabilize adult hippocampal neurogenesis could aid in preventing initial addiction as well as future relapse.

DRUGS OF ABUSE, ADULT NEUROGENESIS AND MEMORY FUNCTION

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Stimulant abuse has negative effects on several cognitive parameters that range from verbal and perceptual abilities to memory capacity. Studies using animal models of human memory processes have confirmed the deleterious consequences of chronic or binge-like stimulant exposure on cognitive function. Both human and animal data uniformly indicate that repeated exposure to stimulants produces maladaptive neuronal adaptations in the hippocampal network and deficits in hippocampal-dependent memory function. In the last decade, the emergence of adult hippocampal neurogenesis has added a new dimension to neuropsychological and neurobiological inquiry into the basis of drug-induced memory impairment. Given the paucity of data on the possible role of hippocampal neurogenesis in the adult human brain, I have used a comparative approach to investigate the contribution of adult neurogenesis to stimulant-induced memory dysfunction. The results of this inquiry indicate that stimulant abuse impacts negatively on at least four areas of memory/cognitive function that may be modulated by adult hippocampal neurogenesis: contextual memory, spatial memory, working memory and cognitive flexibility. We suggest that stimulant-induced impairments in adult hippocampal neurogenesis may contribute in humans to disrupt contextual/episodic memory formation, alter spatial abilities, evoke deficits in working memory function and induce mental rigidity, one cognitive feature that is likely to promote vulnerability to drug addiction.

ENVIRONMENTAL ENRICHMENT AND DRUG ADDICTION

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Environmental enrichment (EE) has been shown to have powerful effects on the brain and to produce beneficial effects on a variety of physiological and pathological processes. Accumulating evidence indicates that EE can mimic positive life experiences and prevent the development of drug addiction. More recently EE has also been shown to eliminate already developed addiction-like behaviours and to reduce the risks of relapse. These preventive and curative effects of EE are associated with dramatic plastic changes in several brain areas such as the hippocampus, the frontal cortex and the striatum. EE alters all neurotransmitter systems, produces changes in gene expression and transcription factors, induces chromatin rearrangement, and stimulates hippocampal neurogenesis. In this talk, we will present recent results that help understanding how EE-induced neuroadaptations result in decreased vulnerability to addiction and relapse. Based on our results and the existent literature, we propose that EE can be seen as a functional opposite of stress. Through its antistress effects, EE would produce brain neuroadaptations that would reduce the reinforcing effects of drugs and their ability to induce long-lasting neuroplastic changes and, thus, it would prevent the development of drug addiction. On the other hand, permanent or transient restoration of the normal, pre-drug functioning of the stress system would facilitate resisting prepotent desire to take drug and it would decrease the risks of relapse.

YOUNG SCIENTISTS

EFFECTS OF IMIPRAMINE AND CITALOPRAM ON PLASTICITY AND BDNF LEVELS IN ASTROCYTIC AND NEURONAL CELL LINES IN VITRO

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Increasing evidence suggests a role for brain-derived neurotrophic factor (BDNF) in atrophy and neurogenesis in relation to affective behavior. Stress and depression decrease BDNF expression and neuronal plasticity while antidepressants reverse or block these effects. Numerous studies indicate that antidepressant efficacy is linked with elevated BDNF-TrkB signaling. In addition, selective loss of BDNF in the dendate gyrus exerts a pro-depressant effect and decreases neurogenesis in rats, and attenuates antidepressant efficacy in mice. In order to study the functional mechanisms of antidepressants in vitro, differentiated mouse neuroblastoma (Neuro-2A) and astrocytic (C8-D1A) cell lines were treated with citalopram, a selective serotonin reuptake inhibitor (SSRI), or imipramine, a tricyclic antidepressant. Plasticity-related morphological features were analyzed together with intracellular and extracellular levels of BDNF. Results suggest that antidepressants enhance plasticity in vitro in both cell lines. In the astrocytic cell line citalopram increased and imipramine decreased intracellular levels of BDNF while extracellular BDNF was unaffected. In the neuronal cell line both antidepressants decreased intracellular levels of BDNF while extracellular BDNF levels were unaffected. In addition, antidepressant treatment was combined with RNA interference to identify essential mediators including Erk, Akt and CREB of the antidepressant action in the BDNF-TrkB signaling cascades. Insight into the exact mechanism of action of antidepressants may reveal more specific targets for the development of novel antidepressant drugs.

DIFFERENTIAL REGULATION OF NEUROGENESIS ALONG THE SEPTOTEMPORAL AXIS OF THE HIPPOCAMPUS

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The hippocampus is involved in both cognitive and emotional processing; these different functions are topographically distributed along its septotemporal axis, the dorsal hippocampus being preferentially involved in cognitive processes such as learning and memory while the ventral hippocampus participates in emotional regulation and anxiety-related behaviours. Newborn hippocampal neurons become functionally integrated into hippocampal networks and are likely to contribute to hippocampal functions, but whether their regulation and function are homogenous throughout this axis is not clear. Here we investigate changes in cell proliferation and neurogenesis in the dorsal and ventral hippocampus induced by the unpredictable chronic mild stress model of depression (UCMS), chronic fluoxetine treatment and enriched environment.

Mice were either subjected to 7 weeks of UCMS, standard housing or enriched environment. Stress-exposed mice were treated daily with fluoxetine (10 mg/kg) from the third week onward. Effects of UCMS regimen and fluoxetine treatment were assessed by physical measures (weight, coat state) and behavioural testing (Splash test, Novelty-Suppressed Feeding test). Behavioural effects of housing were assessed by the Object Recognition Test and the Elevated Plus Maze. Cell

proliferation and neurogenesis changes were respectively assessed by BrdU labelling and double-labelling for BrdU and NeuN.

Results indicate that UCMS decreased cell proliferation and neurogenesis in the ventral hippocampus, an effect that was reversed by fluoxetine treatment. Environmental enrichment preferentially increased cell proliferation in the ventral hippocampus while it promoted neurogenesis mainly in the dorsal hippocampus.

This differential regulation might imply different properties and function of newborn neurons along the septotemporal axis of the hippocampus.

CHARACTERIZATION OF NEUROGENESIS IN THE SHEEP BRAIN

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Production of new neurons continues throughout life in the olfactory system and the dentate gyrus (DG) of the hippocampus. In sheep, maternal behavior appears at parturition and depends on olfaction. Neurogenesis could be involved in the onset of this behaviour. However, in sheep no data on neurogenesis is available.

In the present study, we first investigated the existence of adult cell proliferation in sheep. Newly born cells labelled by the cell proliferation marker 5-bromo-2′-deoxyuridine (BrdU) were found in the SVZ, the DG and more unexpectedly in the main olfactory bulb (MOB), and completely colocalized with Ki67, another mitotic marker. Forty to 50% of the BrdU-labeled cells contained GFAP suggesting the presence of neural stem cells.

Secondly, we characterized cell survival at different times around parturition in the MOB and the DG. Parturient ewes were injected with BrdU 35, 60, or 90 days before sacrifice at 2 days post-partum. Phenotype of BrdU positive cells was characterized with two neuronal markers, NeuN (mature neurons) and DCX (immature neurons), and with a marker of mature glial cells, S100. Immunofluorescent double labeling was analysed with a confocal microscope in 223-542 cells depending on the group and the marker. In the MOB, the proportion of BrdU positive cells co-labelled with NeuN or DCX or S100 significantly increased across time. Similar dynamic of maturation was found in the DG except that the percentage of BrdU+/DCX+ did not significantly vary across time. At day 35 and day 90, percentage of BrdU+/NeuN+, and BrdU+/DCX+ were significantly greater in the DG than in the MOB. Overall, these results indicate that a similar dynamic of maturation is observed in both neurogenic regions with an earlier maturation in the DG. However, the neuronal maturation process appears to be incomplete at day 90 since only around 20% of newborn cells are neurons. Therefore, the neuronal maturation process would be longer in sheep than in rodents and resemble to what is observed in primates. A longer survival time (120 days) is currently studied to support this hypothesis.

ROLE OF 5-HT2B RECEPTOR IN THE CHRONIC EFFECTS INDUCED BY SSRI ANTIDEPRESSANTS

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Chronic effects of selective serotonine reuptake inhibitors (SSRI) antidepressants have been partially linked to sustained increases of serotonine (5-HT) levels, which are controlled by the 5-HT transporter (SERT). Likewise, SERT activity is regulated by different 5-HT receptors subtypes. We thus studied the putative role of 5-HT2B receptors on the chronic effects of SSRI. Mice invalidated for the 5-HT2B receptor (5-HT2B−/− mice) and their wild type (WT; 129/SvPAS mice) received SSRI during 4 weeks. In behavioral tests after acute (forced swimming test) or chronic (novelty suppressed feeding test) SSRI treatment, WT mice developed classical responses, whereas 5-HT2B−/− mice did not respond to either test. Likewise, antidepressant-induced neurogenic effects were only observed in WT mice, but no response was detected in 5-HT2B−/− mice. The increase in hipocampal 5-HT levels induced by acute SSRI was significantly higher in WT mice than in 5-HT2B−/− mice. We then evaluated the BDNF pathway in the hipocampus. BDNF mRNA as well as proBDNF levels were increased in WT mice after SSRI chronic treatment. Surprisingly, 5-HT2B−/− mice have increased basal levels of BDNF mRNA and proBDNF comparing to WT mice. As apoptotic actions have been linked to the proBDNF-p75 pathway, we analyzed apoptotic markers: 5-HT2B−/− mice showed decreased basal Bcl2 levels and increased expression of caspase 3. Altogether, these results confirm that the 5-HT2B receptor is implicated in the effects of SSRI, possibly as a positive autoreceptor controlling SERT activity and determining lower extracellular 5-HT availability after SSRI administration.

Additionally, the absence of neurogenic effects induced by SSRI in mice lacking the 5-HT2B receptor might be due to over-expressed apoptotic signalling. These data suggest as well, an 'antidepressant-like' phenotype in 5-HT2B−/− mice which we are currently further analyzing. The present results support the potential of the 5-HT2B receptor as a possible target in antidepressant pharmacotherapy.

SUGAR OVERCONSUMPTION DURING ADOLESCENCE INDUCES DEPRESSIVE-LIKE BEHAVIOR IN ADULT MALE RATS

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In human, several studies examining diet during adolescence clearly show associations between diet quality and depressed mood in adolescents (Jacka *et al. Am J Psychiatry* 2010). Very few studies, however, have directly investigated the long term impact of diet quality on brain reward system and risk for development of neuropsychiatric disorders later at adulthood. Recently we showed that overconsumption of palatable sweet solution during adolescence had a specific long-lasting effect on motivation and reward function at adulthood in male rats (Vendruscolo *et al. PLoSOne* 2010). Because alteration of motivation for natural rewards (or anhedonia) is a hallmark of depression, we further tested at adulthood, rats pre-exposed or not to sucrose during their adolescence (Post Natal Day 30–46), for expression of several 'depressed-like' behaviors. We showed that, besides having a decreased sensitivity to sweet and non sweet reward, adult rats pre-exposed to sucrose during adolescence also demonstrated an increase of the time spent immobile in the forced-swim test and latency to feed in the novelty-suppressed feeding test. To test whether these long lasting changes in behavior are relevant to depressive-like disorders, we studied the effects of chronic treatment with a tricyclic antidepressant (Imipramine, 10 mg/kg i.p. Post Natal Day 47 onwards). Chronic antidepressant treatment partially reversed the attenuated motivation for saccharin in adult rats pre-exposed to sucrose and reversed the depressive–like behaviors mentioned above. Hence; we showed that sucrose pre-exposure generated decreased neurogenesis in the dendate gyrus which was restaured by the antidepressant treatment. These findings suggest that sugar overconsumption during adolescence induces enduring changes in the brain reward system leading to a depressive-like state. Considering the easy availability and excessive consumption of sugar (especially by adolescents) in our modern societies these findings may have clear implications for the understanding of the epidemic incidence of depression and other reward-related psychiatric disorders.

HIPPOCAMPAL NEUROGENESIS DURING MURINE AND HUMAN ONTOGENESIS: SAME BUT DIFFERENT?

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In many vertebrates including humans neurogenesis in the subventricular zone and in the dentate gyrus (DG) of the hippocampus carries on from the late embryonic stage until old age. Hippocampal adult Neurogenesis (aN) is known to be regulated by a number of factors such as age, acute and chronic stress, enriched environment, physical exercise, learning, seizures, ischemia, and antidepressants and is discussed to be linked to mental disorders such as schizophrenia.

In order to gain better understanding about aN in mice and humans we compared the extent and the distribution of stem cell proliferation during postnatal ontogenesis. For this purpose we carried out an immunohistochemistry (IHC) study using the proliferation marker Ki-67. Moreover, we set out to establish the detection of Doublecortin (DCX), NeuroD and Calretinin-marker proteins expressed by immature differentiating neurons-which can be used for verifying the birth of new neurons in human and murine tissue. Additionally, we performed immunofluorescencedoublelabeling with Ki-67 and DCX, NeuroD as well as Calretinin.

Using the Ki-67 antibody, we were able to demonstrate that in both species DG stem cell proliferation decreases with age, but that the distribution pattern of proliferating cells differs in these two species. This age-dependency could also be shown by IHC on murine tissue slices using antibodies against NeuroD, DCX and Calretinin. IHC on human tissue however did not result in specific labeling. In search for possible reasons we performed a specific post-mortemdelay (PMD) study. Using tissue slices of this PMD study, we could verify that the antigen of DCX is susceptible to an over three-hour post-mortem-delay (PMD) and found that the same applies to NeuroD. This finding forms a feasible explanation for the fact that neither DCX nor NeuroD can be successfully used as aN makers in human brain tissue with PMDs of several hours.

ALPHA2-DELTA LIGANDS PROMOTE ADULT NEUROGENESIS IN VITRO VIA NF-κB SIGNALING

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Although the role of adult neurogenesis remains to be fully elucidated, several studies suggested that the process is deregulated in various neuropsychiatric disorders. Additionally, some psychoactive drugs (antidepressants, mood stabilizers, antipsychotics) can positively affect adult neurogenesis, opening the exciting possibility of its pharmacological modulation as a therapeutic strategy in CNS diseases. We investigated the potential activity of the anticonvulsants carbamazepine, oxcarbazepine, gabapentin (GBP), pregabalin (PGB), mephenytoin and ethosuximide on differentiation toward the neuronal lineage of adult mouse neural progenitor cells (NPC). Among all drugs, only PGB and GBP resulted in a concentration-dependent increase in the number of newborn mature and immature neurons generated from adult NPC, and in parallel a decrease in the number of undifferentiated precursor cells. Similar results were obtained with valproic acid (VPA), that is known to promote neurogenesis in vitro and in vivo. PGB and GBP concentrations which were active on neuronal differentiation of adult NPC closely correlated with drug binding affinities for the auxiliary alpha-2-delta (α2-δ) subunit of neuronal voltage-gated calcium channels. Indeed, the α2-δ antagonist L-isoleucine counteracted PGB and GBP effects in a concentration-dependent manner, suggesting the involvement of the α2-δ subunit in the drug-mediated actions on NPC differentiation. Finally, we documented that NF-κB signaling was involved in the PGB- and GBP-mediated effects, both by inhibiting nuclear translocation of the family member p50 or by taking advantage of NPC derived from p50−/− mice. In conclusion, here we demonstrated a novel pharmacological property of α2-δ ligands, namely positive modulation of adult neurogenesis via NF-κB signaling.

POSTERS

SHORT-TERM EFFECTS OF AN AUDITORY STRESS ON BEHAVIOR, THE ACTIVITY OF THE HPA AXIS, AND CARDIOVASCULAR REGULATION

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The aim of our study was to evaluate the effects of a short auditory stress on some stereotypic behaviors of Wistar rats and on cardiovascular regulation and activation of the HPA axis (ACTH).

The auditory stress 15 min caused a reduction in the number of exploring and an increase in the number of freezing which persist even after cessation of noise. This same stress caused an elevation of plasma ACTH (22.2 ± 6.76 vs. 45.4 ± 9.05 pg/ml), elevated mean arterial pressure (83.8 ± 5.1 vs. 96.2 ± 3.8 mmHg) and heart rate (442.5 ± 9.4 vs. 475.0 ± 14.5 beat/min).

These results highlight the animal facility of a state of fear caused by the noise.

Repeating the same homotypic stress for 7 consecutive days, do not give the same answers. At the behavioral level there is a disappearance of freezing and a decrease in the exploring. Mean arterial pressure returned to its baseline (83.8 ± 5.1 vs. 80.3 ± 3.2 mmHg) and heart rate (442.5 ± 9.4 vs. 394.4 ± 23.2 beat/min) while the ACTH is no longer a significant change (22.2 ± 6.76 vs. 37.9 ± 6.2 pg/ml).

The sleeping/resting on the rearing and grooming were unchanged in the short auditory stress.

These results reflect the installation of the phenomenon of habituation, during which the animal becomes insensitive to auditory stress. The mechanisms by which these responses take place remains to be determined.

EFFECTS OF MODAFINIL ACUTE DOSES ON MOUSE AGONISTIC BEHAVIOUR

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Modafinil is a wake-promoting drug approved for treatment of neuropsychiatric conditions characterised by excessive sleepiness. Although it appears to be well tolerated in most of the patients without serious adverse effects, its actions need to be studied closely, because its use is becoming often also in healthy people, who use it off-label in attempt to increase their cognitive functions and repress their need to sleep. So far there is a lack of studies focused on effects of modafinil on affectivity. The aim of our study was evaluate influence of modafinil on agonistic behaviour in animal model.

Behaviour was analysed in singly-housed male mice on paired interactions with non-aggressive group-housed partners. Recorded were sociable, defensive-escape, aggressive and locomotor behavioural elements. We analysed aggressive and timid mice separately. Mice were administered modafinil at the doses of 2 or 10 or 50 mg/kg, or saline intraperitoneally, 30 min prior to interactions provided 7 days apart.

Paired interactions were videotaped and ethological observation was performed by the experimentator using the system Observer (Noldus Technology, Holland). Data were analyzed using two-way ANOVA.

In timid mice, modafinil at the doses of 2 and 10 mg/kg decreased timidity; sociable activities were not significantly changed; at the doses of 10 and 50 mg/kg increase of locomotion was measured.

In aggressive mice, modafinil at the doses of 2 and 10 mg/kg selectively decreased aggressivity; the dose of 50 mg/kg increased locomotion and decreased social behaviour with no effects on aggressive acts; defensive-escape activities were not significantly influenced by modafinil.

The psychostimulant effects of modafinil were confirmed in the present design only at the highest dose tested. Besides that however modafinil at the lower doses exhibited also anxiolytic-like (decrease of escape-defensive acts) and antiaggressive-like effects in timid and aggressive mice, respectively. Supported by Czech Ministry of Education: MSM0021622404.

EFFECTS OF CHRONIC FLUOXETINE TREATMENT ON OREXINERGIC NEURONAL ACTIVATION AND OREXIN-RECEPTOR 2 EXPRESSION IN A MOUSE MODEL OF DEPRESSION

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Chronic stressful life events are risk factors for depression often accompanied by homeostatic disturbances. Hypothalamic neuropeptide orexin is involved in regulation of several autonomic functions that are altered in depression. However, little is known about the link between orexinergic systems and depression. Using double immunohistochemical labeling for orexin-containing neurons and Fos protein, we studied the effect of a chronic SSRI antidepressant treatment (fluoxetine, 20 mg/kg/day, i.p.) on the orexin neuronal activation in mice exposed to unpredictable chronic mild stress (UCMS), a rodent model of depression. Western blot was also performed to assess orexin receptors expression in eight brain areas: prefrontal cortex, ventral and dorsal hippocampus, amygdala, thalamus, hypothalamus, midbrain and brain stem. UCMS induced physical disturbances with deterioration in coat state and reduced weight gain. Increase of agonistic and despair behaviors, as well as lack of motivation, were respectively seen in resident-intruder test, tail suspension test and nest building test. All UCMS effects on physical and behavioral parameters were reversed by chronic fluoxetine treatment. Immunohistochemical analysis demonstrated that orexinergic neurons were more activated in the perifornical and dorsomedial area (PFA-DMH) of UCMS-subjected mice compared to the lateral hypothalamus (LH), and this increase was reversed by chronic antidepressant treatment. UCMS also reduced expression of orexin-receptor 2 (OXR2) in the thalamus and hypothalamus, but not in animals chronically treated with fluoxetine. In addition, chronic fluoxetine administration induced an increase of OXR2 expression in prefrontal cortex, specifically in UCMS-subjected mice. These data suggest that orexin neurons in the PFA-DMH may contribute to the pathophysiology of depressive disorders through OXR2.

THE P50 MEMBER OF THE NF-κB FAMILY REGULATES ADULT NEUROGENESIS IN THE HIPPOCAMPUS AND NOT IN THE OLFACTORY BULB

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Neurogenesis proceeds throughout adulthood in two restricted brain regions, the Subventricular zone (SVZ) and the subgranular zone (SGZ). Apparently, the two neurogenic regions share some modulatory mechanisms but also respond differently to drugs, with the SGZ being stimulated by antidepressants and atypical antipsychotics and the SVZ by typical antipsychotics. Alterations in adult neurogenesis have been observed in several neuropsychiatric disorders where disregulated NF-kappaB signalling also occurs. We have investigated both hippocampal and olfactory bulb (OB) neurogenesis in p50-deficient (p50−/−) mice and wt littermates. We demonstrated that in hippocampus absence of p50 does not affect the net rate of neural precursor proliferation, while some of the steps leading postmitotic new neurons to the final differentiation status are hampered, resulting in approximately 50% reduction in the overall number of newborn neurons. To further dissect these alterations, we examined newly generated neuronal cells in immature and postmitotic stages using the protein markers Doublecortin (DCX) and Calretinin (CR), respectively. No difference was demonstrated in the number of DCX+ cells while a significant reduction in the number of CR+ cells was observed in p50−/− compared to wt mice. This reduction was also confirmed by Western blotting where the level of CR expression was reduced of 56% in p50−/− mice. Quite surprisingly, DCX expression levels were significantly reduced (−47%) in p50−/− mice. When we moved to investigate OB neurogenesis, no difference was detected both in the proliferation rate and survival of newly generated cells. Moreover, the expression levels of markers of immature and postmitotic neuroblasts were not significantly different in the two genotypes. In conclusion, we propose that NF-kappaB p50 protein has a specific modulatory role on adult neurogenesis in the hippocampus but not in the OB. The contribution of this signalling pathway to the region-selective proneurogenic effects of neuropsychiatric drugs deserves further investigation.

IMPAIRED EXTINCTION OF CUE-, BUT NOT CONTEXT-, INDUCED FEAR IN THE SEROTONIN TRANSPORTER KNOCKOUT RAT: THE ROLE OF THE HIPPOCAMPUS

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The phylogenetically ancient and highly conserved serotonergic system plays a key role in fear learning. As such, the low activity (short) variant of the common serotonin transporter (5-HTT) polymorphism (5-HTTLPR) confers increased sensitivity to aversive stimuli and paves the path for psychopathologies in the context of stress. These phenotypic manifestations are linked to functional and anatomical disturbances in a corticolimbic neurocircuit involving the prefrontal cortex (PFC) and amygdala. Besides the PFC and amygdala, the hippocampus is involved in fear learning. While the 5-HTTLPR short variant has also been linked to hippocampal changes, the nature and behavioural correlates of these hippocampal changes are unclear thus far.

In analogy with the human findings. serotonin transporter knockout (5-HTT−/−) rodents show increased fear- and stress-related behaviors and morphological changes in the PFC and amygdala. We used 5-HTT−/− rats to investigate the effects of genetically driven loss of 5-HTT function for cue- and context-induced fear extinction and immunoreactivity of the immediate early gene c-Fos. In separate groups of animals we also measured neurogenesis (doublecortin immunoreactivity) and brain-derived neurotrophic factor (BDNF) expression (mRNA protection assay) in the hippocampus. Extinction of cue-induced, but not context-induced, fear conditioning was impaired in 5-HTT−/− rats. Preliminary data suggest that this extinction failure was associated with a decreased c-Fos immunoreactivity in the infralimbic part of the PFC and the hippocampal dendate gyrus, but no change in the amygdala of 5-HTT−/− compared to wild-type (5-HTT+/+) rats. We also observed that BDNF expression

was decreased in the PFC and hippocampus of 5-HTT−/− animals. Measurements of neurogenesis are currently in progress and will be presented. In conclusion, these preliminary data suggest that the hippocampus is involved in a neurocircuit involving the PFC and amygdala mediating fear-related behaviors in association with loss of 5-HTT gene function. The potential relationship with neurogenesis will be discussed.

LITHIUM-INDUCED INCREASES IN CELL PROLIFERATION ARE RESTRICTED TO THE VENTRAL HIPPOCAMPUS IN STRESSED BALB/C MICE: RELATIONSHIP TO CELL SURVIVAL

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Antidepressants and the mood stabiliser, lithium, have been shown to increase adult hippocampal neurogenesis. Accumulating evidence suggests that the hippocampus is functionally divided into dorsal (dHi) and ventral regions (vHi) and that the vHi preferentially regulates emotionality and the stress response while the dHi is primarily involved in cognitive function. The present study investigated whether chronic immobilisation stress and/or chronic treatment with lithium would alter cell proliferation and survival along the septo-temporal axis of the hippocampus in a stress-susceptible mouse strain, the BALB/c mouse.

Lithium increased hippocampal cell proliferation but only in stressed animals. Moreover, the stress x lithium-induced increase in cell proliferation occurred in the vHi but not the dHi. Further, both stressed and non-stressed mice demonstrated lithium-induced decreases in the survival of cells that were newly-born prior to experimental treatment. Moreover, lithium reduced cell survival in the dHi of both stressed and non-stressed mice and significantly reduced cell survival in the vHi of the stressed group only.

Taken together, these data suggest that lithium-induced increases in hippocampal cell proliferation might only occur when hippocampal function is confronted with adverse challenges such as stress. The localization of lithium-induced cell proliferation to the vHi of stressed animals further supports the hypothesis that the vHi plays a preferential role in processes relevant to stress-related disorders. Finally, the lithium-induced increase in cell proliferation suggests a compensatory response to decreases in the survival of newly-born cells. Therefore, lithium increases cell turnover rather than cell proliferation per se. These findings underscore the necessity for determining the effects of experimental treatments not only on cell proliferation but also on the survival of pre-existing newly-born cells.

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THE EFFECTS OF PRENATAL VALPROIC ACID ON ADULT NEUROGENESIS IN A MOUSE MODEL FOR AUTISM

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Autism Spectrum Disorders (ASD) are developmental disorders characterised by impaired social interaction skills, communication problems, and repetitive behaviour. Human studies have addressed the contribution of genetic and environmental factors to the aetiology of autism, but preclinical models are also required to investigate disease pathology. The anticonvulsant valproate (valproic acid; VPA) is a reported risk factor for autism when used during pregnancy around the time of neural tube closure. This gestational phase is a critical period for embryonic neurogenesis, and since VPA alters the kinetics of developmental neurogenesis this will ultimately affect the establishment of germinal neurogenic zones in adult brain. In rats, VPA administration to pregnant dams at the corresponding time of embryonic development produces a behavioural and neuroanatomical phenotype closely resembling some aspects of autism in humans. To establish a mouse model of ASD and explore gene–environment interactions, we administered VPA (600 mg/kg) or vehicle on embryonic day 13 to pregnant CD-1, C57Bl/6 and BALB/c mice. Here we report the effects of prenatal VPA treatment on neurological and behavioural scores at multiple time points during development, and on adult germinal zone neurogenesis. This preclinical model might provide several clinically relevant endpoints to study ASD.

EXPOSURE IN FETUS OF METHYLAZOXYMETHANOL IN THE RAT ALTERS BRAIN NEUROTROPHINS' LEVELS AND BRAIN CELLS' PROLIFERATION

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Changes during gestation have been shown to induce brain maldevelopment associated withchanges in neurotrophins as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF)and neuropsychiatric disorders in humans. A rat model of altered prenatal brain development resembling the onset of schizophrenia has been obtained by administering in fetusmethylazoxymethanol (MAM) at gestational day 12 which impairs the growth of limbic pathways between the entorhinal cortex and the hippocampus. Using the MAM model we studied in youngrats the brain levels of both NGF/BDNF and their main receptors, TrkA/TrkB, to investigate whether or not changes in neurotrophins could affect the presence of brain BrdU positive cells. We found increased NGF and BDNF protein levels, associated with elevated TrkA and TrkB expression, in the hippocampus, entorhinal cortex, olfactory lobes and subventricular zone (SVZ), brain areas playing a key role in the production and migration of new dividing cells. We also found higher levels of BrdU positive cells in the SVZ and hippocampus but not a significant potentationin the entorhinal cortex and olfactory lobes. All together the findings indicate that prenatal MAM exposure in young rats may elicit both neurotrophins' elevation and cell proliferation in limbic brain areas.

SEXUAL DIFFERENCES IN THE EFFECT OF ACUTE METHAMPHETAMINE ON SOCIAL INTERACTION IN RATS

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In our previous study we demonstrated that methamphetamine (MA) administration reduces social interaction in a dose- and stress environment condition-specific manner. The aim of the present study was to investigate if male and female gonadal hormones influence the effect of MA on social interaction (SI). Adult gonadectomized male and female Wistar rats were divided into groups with subcutaneous (s.c.) administration of testosterone, estradiol or oil. Each group was tested for SI in an Open field arena. Thirty minutes prior to testing, rats were administered MA (1 mg/kg) or saline (S) s.c. SI of two strange animals with the same pretreatment and hormonal condition was recorded for 5 min and manually analyzed by using ODLog software. Duration and frequency of social and non-social activities were evaluated. Our results showed that MA decreased total SI in both sexes. Sexual differences were observed for mutual sniffing, so that females sniffed less than males. However, this difference was not observed in rats pretreated with MA. Moreover, we found that estradiol increased genital investigation and vertical activity in control female rats while these changes were not present in MA pretreated females. On the other hand, testosterone did not alter either social or non-social behavior in males. In conclusion, our

present study demonstrated that MA decreases SI regardless of sex and diminishes the differences in SI caused by female gonadal hormones.

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THE EFFECT OF REPEATED ADMINISTRATION OF MDMA ON THE NOVEL OBJECT RECOGNITION TEST AND PASSIVE AVOIDANCE TASK

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One of the most commonly abused drugs is 3,4-methylenedioxymethamphetamine (MDMA; ecstasy). MDMA leads to serotonin (5-hydroxytryptamine; 5-HT) neurotoxicity and has been linked to cognitive impairments. It remains unclear whether these impairments are due to MDMA alone or the abuse of other drugs in combination.

The aim of this study is to present the effect of a repeated 4-day administration of MDMA (2.5 and 5 mg/kg s.c. for 4 days) on cognitive tasks in rats. The last injection of MDMA was 4 h before beginning of experiment. Male Wistar rats performed two different cognitive tests: Novel Object Recognition Test (NORT) and Passive Avoidance Task (PAT). NORT measures the exploration of novel versus familiar objects, which is a component of recognition memory and concentration.

A one-trial passive avoidance test assesses a rat's short-term and long-term memory by measuring the time taken for the subject to move from a white compartment to a black compartment. The latency of the rat to return to the dark compartment is measured 90 min and 24 h after the administration of the shock.

MDMA increases spontaneous exploratory activity of a novel object, depending on the dose. In regards to MDMA, it could explain how recognition memory is not disrupted and whether MDMA increased novelty-seeking behavior.

An effect of MDMA was found to worsen performance on the PAT. Rats given MDMA returned more often and more quickly to the dark compartment than the control group. This effect was found both 90 min and 24 h after the administration of the shock condition, which suggests an the inhibition of both short- term and long-term memory.

We suggested that MDMA did not influence recognition memory, but decreased learning of passive avoidance.

INCREASED ADULT HIPPOCAMPAL NEUROGENESIS AND PERSISTENT HIPPOCAMPUS DEPENDENT FEAR MEMORY IN A GENETIC ANIMAL MODEL FOR DEPRESSION

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Adult hippocampal neurogenesis has been implicated in the pathophysiology of major depressive disorder, but little is known about the functional contribution of new dentate gyrus neurons to depressive behavior. Neurogenesis has been shown to play a role in the acquisition and consolidation of fear memories centrally important in stress related disorders such as major depression. We investigated adult hippocampal neurogenesis and characterized hippocampus-dependent contextual fear conditioning in rats bred for learned helplessness, a genetic animal model of depression.

Surprisingly, congenitally helpless rats rats showed no difference in the rate of proliferation or in fate choice of newborn cells and contrary to our expectation, survival of newborn cells and net neurogenesis was not decreased but instead increased in congenitally helpless rats if compared to congenitally not helpless rats. Correspondingly, contextual freezing was significantly increased in congenitally helpless rats four weeks after conditioning, at a time point when persistent associative fear memories are reorganized in neocortical networks in a neurogenesis-dependent process. The increase of newborn neurons in the dentate gyrus of congenitally helpless rats may thus underly increased persistent fearful memories which subsequently contribute to depressive-like behavior.

While these results do not support the hypothesis of a reduced number of newborn neurons underlying depressive-like behavior, they shed light on the function of newborn neurons in the etiology of major depressive disorder and may be the basis to develop innovative biological and psychological antidepressant treatment.

EFFECT OF GABAERGIC DRUGS ON AUDITORY DISCRIMINATION TASK IN RATS

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In schizophrenia patients, both difficulties in speech discrimination and auditory hallucinations have been functionally associated with impaired bottom-up information processing within the sensory auditory cortex. Extensive behavioral training has been reported to ameliorate at least partly these sensory deficits in schizophrenic individuals and to sharpen auditory performance in healthy subjects. Given that the cortical processing of stimulus discrimination is dependent on GABAergic functioning and knowing that there are consistent reports on cortical GABAergic deficits in schizophrenia, goal of the present study was to characterize the ability of several GABAergic compounds such as the benzodiazepine site agonist chlordiazepoxide, benzodiazepine antagonist flumazenil, and non-benzodiazepine GABA-A receptor agonist gaboxadol to affect frequency change discrimination (FCD) of auditory stimuli. A group of 24 adult rats was extensively trained to perform the FCD task in operant boxes equipped with a nose-poke detector, a sound generator, two levers and a food dispenser. Rats were trained to discriminate changes in the 78-dB auditory stimuli from a reference baseline frequency (3000 Hz) to a target frequency (ranging from 2000 to 2970 Hz). After three months of training, performance accuracy of 22 animals gradually reached the level of 85% correct responses per session that enabled drug treatment studies. We found that flumazenil (up to 10 mg/kg) and gaboxadol (up to 20 mg/kg) had no specific effects on FCD performance, whereas chlordiazepoxide (10 mg/kg) significantly enhanced auditory discrimination accuracy. Ongoing studies evaluate other psychoactive compounds for their potential impact on FCD and the effects of auditory discrimination training on neurogenesis and cortical GABAergic markers.

EFFECTS OF ENVIRONMENTAL ENRICHMENT ON THE INCUBATION OF COCAINE CRAVING

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In addition to the known preventive effects against drug addiction, exposure to environmental enrichment (EE) during withdrawal periods may also have 'curative' effects and reduce the risks of relapse in rats. In this study, we investigated whether EE would reduce incubation of cocaine craving, i.e. the increase in cocaine-seeking behaviour found after long periods of withdrawal. For this, we (1) trained singly-housed rats to self-administer cocaine for ten days; (2) measured cocaine-seeking after 1 day of withdrawal; (3) separated rats in social standard conditions (SE) or EE and kept them abstinent from drug for 30 days and (4) tested rats

for cocaine-seeking in order to measure incubation of craving. To further investigate whether incubation could be reduced by EE once developed and whether the effects of EE would last after discontinuation of enriched housing, we switched half of SE rats to EE and half of EE rats to SE, kept them in the animal facility for one month and tested them again for cocaine-seeking behaviour. We found that exposure to EE reduced cocaine-seeking behaviour only when actual exposure to EE preceded drug-seeking tests. On the other hand, rats that were initially exposed to EE but then were switched to SE show levels of cocaine-seeking that are similar to those of control rats that were kept in SE for the entire duration of the experiment. These results indicate that EE can reduce cocaine craving but only as long as EE is provided and that the beneficial effects of EE are lost with discontinuation of enrichment.

POSSIBLE EFFECT OF NARINGIN A CITRUS FLAVONOID, AGAINST COLCHICINE INDUCED COGNITIVE DYSFUNCTION AND OXIDATIVE DAMAGE IN RATS

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Alzheimer's disease (AD) is a neurodegenerative disorder. Central administration of colchicine is well known to cause cognitive impairment, oxidative damage which simulates sporadic dementia of Alzheimer type in humans. Present study has been designed to investigate the protective effects of naringin against the colchicine-induced cognitive impairment and oxidative damage in rats. Colchicine (15 μg/5 μl), was administered intracerebroventricularly that resulted in poor memory retention in both Morris water maze, elevated plus maze task paradigms and caused marked oxidative damage. It also caused a significant decrease in the acetyl cholinesterase activity. Naringin (40 and 80 mg/kg, p.o.) treatment was given daily for a period of 25 days beginning 4 days prior to colchicine administration. Chronic treatment with naringin caused significant improvement in the cognitive performance and attenuated oxidative damage as evidenced by (lowering of malondialdehyde, nitrite concentration, and restoration of superoxide dismutase, catalase, glutathione-s-transferase and reduced glutathione levels) and acetylcholine esterase activity as compared to control. Present study highlights the therapeutic potential of naringin against colchicine-induced cognitive impairment and associated oxidative damage.

GABAB RECEPTOR BLOCKADE INDUCES ANTIDEPRESSANT-LIKE BEHAVIOURAL EFFECTS: RELATIONSHIP WITH NEUROGENESIS

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Although aberrations in GABA neurotransmission have long been implicated in the pathophysiology of mood disorders, the role of metabotropic GABAB receptors in depression is not well defined. Recent evidence demonstrates that GABAB receptor antagonists via interaction with the serotonergic system, display antidepressant-like properties and therefore, represent a novel approach for the treatment of depression. Chronic treatment with different classes of antidepressant drugs increases neuronal proliferation in dentate gyrus of the adult hippocampus, thus suggesting a role for hippocampal neurogenesis in their mechanism of action. In the present study, we investigated the effects of the high affinity GABAB antagonist, CGP52432, in a behavioural test of antidepressant drug-like activity, the forced swim test (FST), as well as its effects on neurogenesis in the adult hippocampus. BALB/c mice were acutely treated with CGP52432 (3, 10, 30 mg/kg i.p.) and were tested in the FST 30 min later. All doses of CGP52432 significantly reduced immobility in the FST, thus suggesting an antidepressant-like behavioural effect. To determine the effects of CGP52432 on hippocampal neurogenesis, mice were chronically treated with CGP52432 (3, 10 mg/kg i.p) for 21 days and these mice were also tested in the FST. Chronic treatment with CGP52432 dose-dependently decreased immobility in the FST. Moreover, preliminary analysis of BrdU immunohistochemistry suggests that chronic treatment with CGP52432 may increase cell proliferation in the dentate gyrus. Taken together, this data demonstrates that GABAB receptor modulation can induce antidepressant-like effects both in behaviour and possibly in hippocampal neurogenesis. This study can advance our understanding in the neurobiological basis of depression and its treatment. Supported by FP7-DEVANX – HEALTH-F2-2007-201714 (JFC) and the Health Research Board Ireland PD/208/26 (OFO).

INVOLVEMENT OF POSSIBLE NITRIC OXIDE MECHANISM IN THE PROTECTIVE EFFECT OF HESPERIDIN AGAINST ISCHEMIC REPERFUSION CEREBRAL INJURY USING EXPERIMENTAL MODEL OF STROKE

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The present study was conducted with a aim to explore the role of hesperidin and its nitric oxide mechanism against ischemia reperfusion induced- neurobehavioral alterations, oxidative damage and cellular in rat brain. Male Wistar rats (200–220 g) were subjected to bilateral common carotid artery occlusion for 30 min followed by 24 h reperfusion injury. Animals were pretreated with hesperidin {HES} (50, 100 mg/kg, p.o.) for 7 days before subjected to 30 min ischemia and 24 h reperfusion injury. Various behavioral tests [locomotor activity, neurological score (inclined beam test), rota-rod, transfer latency, resistance to lateral push] and biochemical parameters (lipid peroxidation, nitrite level, reduced glutathione, superoxide dismutase and catalase activity), mitochondrial enzyme dysfunctions (Complex I, II, III and IV) in cortex and striatum were assessed subsequently. Seven days hesperidin (50 and 100 mg/kg) pretreatment significantly improved neurobehavioral alterations (improved locomotor activity, inclined beam walking and reduced resistance to lateral push, transfer latency), attenuated oxidative damage, restored mitochondrial enzyme activities in cortex and striatum areas in ischemic brain as compared to control (I/R) animals. Further, L-NAME pretreatment with sub-effective dose of hesperidin (50 mg/kg) caused significant potentiation in neurobehavioral, biochemical and mitochondrial effects as compared to their effect per se. However, L-arginine pretreatment with sub effective dose of hisperidine reversed the protective effect of hisperidin in all the parameters.

Present study suggests that nitric oxide modulation might be involved in the protective effect of hisperidin against ischemia reperfusion induced alterations in rats.

IMPAIRED CONTEXTUAL FEAR EXTINCTION IN A SPONTANEOUS RAT MODEL OF DEPRESSION: A ROLE FOR NEUROGENESIS IN PERSISTENT NEGATIVE COGNITIVE PROCESSING?

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Affective processing in depressed patients is biased towards negative stimuli, thus interfering with optimal cognitive processing. Impairment of cognitive functions is a core symptom of the pathology, weakly addressed in preclinical models of depression. The stress-sensitive Wistar-Kyoto rat strain (WKY) has been proposed as a putative genetic model of depression. In this study, we address this point and try to understand behavioral and cellular mechanisms underlying these strain differences. We present evidence that adult WKY compared to Wistar

rats exhibit normal fear learning but impaired contextual extinction performances, associated with high spontaneous despair-related behavior in the forced swim test. Recent findings suggest that between-session extinction better reflects long-term re-learning mechanisms than within-session extinction, and also propose that adult hippocampal neurogenesis facilitates memory reorganization. We are currently investigating the cellular mechanisms underlying persistence of negative processing of contextual stimuli in this model. Our data suggest that the WKY strain could potentially serve as a highly relevant model of cognitive impairments associated with depression.

NF-κB PROTEINS AS POTENTIAL TARGETS FOR PHARMACOLOGICAL MODULATION OF HIPPOCAMPAL NEUROGENESIS

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In the adult neurogenic niches multipotent stem/progenitor cells self-renew and give rise to precursors cells, some of which differentiate into neurons which functionally integrate in the pre-existing circuit. In this favourable microenvironment, the close interactions of stem/progenitors cells with transient precursors suggest that they continue to interact with their progeny, possibly exchanging signals that are important for their subsequent differentiation and maturation. In such respect NF-κB proteins may represent ideal candidates for translating signals in the highly specialized neurogenic niche. We first demonstrated the presence of distinct NF-κB family members in specific cell populations of the adult SVZ and SGZ regions, thus suggesting their contribution to signalling pathways involved in postnatal neurogenesis. More recently, we investigated hippocampal neurogenesis in NF-κB p50KO mice and demonstrated a selective defect in this process in absence of the protein, compared to wt mice. Since adult hippocampal neurogenesis has been implicated in learning and memory, mutant and wt animals were also analyzed for their cognitive performance in hippocampal-dependent spatial memory tasks. A selective defect in short-term spatial memory performance was observed in p50KO mice without impairment of hippocampal-dependent spatial long-term memory and learning. Additionally we demonstrated that NF-κB signalling is indeed crucial for differentiation of adult neural stem/progenitor cells toward the neuronal lineage in response to selected psychotropic drugs and to activation of surface receptors. Several neuropsychiatric disorders have been associated with alterations in both neurogenesis and NF-κB-mediated transcription, but no attempt has ever been made to correlate these phenomena. The possibility that disregulated NF-κB signalling may contribute to altered neurogenesis as well as cognitive impairment in such disorders and therefore represent a potential target for pharmacological modulation of hippocampal neurogenesis is proposed.

NEUROPROTECTIVE EFFECT OF MK-801 AGAINST INTRA-STRIATAL QUINOLINIC ACID INDUCED BEHAVIORAL, BIOCHEMICAL AND HISTOLOGICAL ALTERATIONS IN RATS

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Background and aim: Huntington Disease (HD) is a common neurodegenerative disorder characterized by motor disturbances. Pathogenesis of HD so far revolves around excitatory amino acids as primary cause of neuronal loss. Several recent reports suggests the involvement of excitotoxicity and oxidative damage. In the present study, first the dose of quinolinic acid that mimics the symptoms of HD was standardized and then the neuroprotective effect of MK-801 (noncompetitive NMDAr antagonist) was evaluated against intrastriatal quinolinic acid induced behavioral, biochemical and histological alterations in rats.

Methods: A single unilateral injection of quinolinic acid (100, 200 and 300 nmol/l) were made in to striatum. Animals were tested for motor functions using actophotometer and rotarod apparatus. On day 21st after behavioral assessment animals were sacrificed and brains were removed, cortex and striatum were isolated for different biochemical estimations.

Results: Quinolinic acid (300 nmol/l) significantly reduced body weight and caused motor incoordination and produced biochemical alterations in the cortex and striatum (increased lipid peroxidation, nitrite concentration, depletion of superoxide dismutase, catalase and different glutathione levels). Beside, quinolinic acid (300 nmol/l) significantly altered the mitochondrial enzyme complex levels and caused histopathological alterations in the striatum. MK-801 (0.02, 0.04, 0.08 mg/kg, i.p.) treatment significantly improved body weight, behavioral alterations (locomotor activity and rotarod performance) and attenuated oxidative damage and mitochondrial enzyme complex dysfunction. Besides, MK-801 treatment significantly reversed histopathological alterations in striatum.

Conclusion: The results suggest antioxidant and neuroprotective action of MK-801 against the quinolinic acid induced Huntington like behavioral, oxidative stress and cellular alterations in rat.

DOES 5-HT2C ACTIVATION MEDIATE ANY OF THE DOI-INDUCED BEHAVIORS IN RATS?

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Behavioral changes after DOI (2,5-dimethoxy-4-iodoamphetamine), an 5-HT2A/2C receptor agonist challenge is a well established animal model mainly used to detect 5-HT2A mediated responses (head twitch and wet dog shake), but little is known about the role 5-HT2A/C receptors in other observed behaviors. Previously it was found in rabbits that head bobbing and body shake was 5-HT2A and 5-HT2C receptor-mediated, respectively (Dave, 2002). Our aim was to investigate 5-HT2 antagonists on DOI induced behavior in order to distinguish 5-HT2A and 5-HT2C receptor activation in rats.

Rats (Wistar) were pretreated (30 min) subcutaneously with the 5-HT2A antagonist MDL 100 907, the 5-HT2C antagonist SB-242084 or vehicle, and just before measurement DOI (1 mg/kg) or vehicle were administered intraperitoneally. Behavior of rats was video recorded for 30 min and scored later by two independent observers with Etholog software. Beside the frequently measured behavioral parameters as head twitch (HT), wet dog shake (WDS) and head shake (HS), we also scored head bobbing (HB) and back muscle contraction (BMC).

DOI alone produced characteristic changes in the behavior of rats which included the increase of HS, HB and BMC. WDS and HT were not increased significantly. The selective 5-HT2A antagonist MDL-100 907 (0.01 mg/kg s.c.) significantly inhibited HS, HB and BMC. On the other hand, the 5-HT2C selective antagonist SB-242084 (1.5 mg/kg s.c.) did not inhibit significantly any parameters measured.

Our results showed that 5-HT2A selective antagonist MDL-100 907 inhibited all type of DOI induced stereotype behaviors. Interestingly, in our study no considerable head twitch response was detected after 1 mg/kg DOI in rats. In contrast to previous findings with the same dose of DOI in rabbits, we could not detect 5-HT2C receptor mediated activation even though broad range of behaviors was recorded.

SWITCH FROM POSITIVE TO NEUTRAL LIVING ENVIRONMENTS INCREASES VULNERABILITY TO COCAINE

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Life experiences, especially during early stages of life, can dramatically determine vulnerability to diseases at adulthood. Early exposure to positive environmental conditions such as enriched environments (EE) reduces the occurrence and the intensity of neurological and psychiatric disorders including addiction to drugs. However, it is not known whether exposure to environmental enrichment during early stages of life would protect from addiction even when, at adulthood, individuals may find themselves in non-enriched conditions. To answer this question, mice were reared in EE from weaning until adulthood and then switched to non-enriched standard environments (SE). Development of conditioned place preferences (CPP) to cocaine (10 mg/kg) was investigated 7, 30 and 90 days after this switch of environmental conditions. We found that switching mice from EE to SE not only eliminated EE-induced reduction of cocaine effects but instead increased cocaine-induced CPP. Our results indicate that not only beneficial effects of early exposure to EE do not last over time, but even that depriving individuals of enrichment results in increased rewarding effects of cocaine. Therefore positive life conditions during early stages of life, if they are not maintained at adulthood, may have negative influences on the risks to develop drug addiction. We hypothesise that this deprivation effects are associated with a negative emotional state caused by the change from positive to neutral environments. Therefore, we are currently investigating whether altered expression of the type-1 receptor for CRF in the amygdala may be responsible for the increased sensitivity to cocaine's rewarding effects.

IMPLICATION OF HUNTINGTIN IN MOOD DISORDERS: BEHAVIOR AND NEUROGENESIS STUDY

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Huntington's disease (HD) is a rare autosomal dominant inherited neurodegenerative disorder that affects about 6000 people in France. Psychiatric manifestations are a major component of the early symptoms of HD, among which depression and anxiety are commonly reported during the early, pre-motor symptomatic stages. The prevalence of depression within the HD population has been estimated to range between 30 and 50%. The reasons for the increased incidence of depression in HD remain unclear. The gene responsible for this disease codes a protein called huntingtin (Htt), within sequence is an polyglutamin expand (polyQ). When this expand exceed 40 glutamins, the synthesized protein induces HD developpement.

The aim of this study was the characterization of an original model of Huntington mice, HdhQ111 mice, in a behavioral as well as biochemical way. We studied neurogenesis and BDNF expression in the hippocampus, and verified whether these mice present an anxious or depressive phenotype, and if there is variations with mice sex.

As observed in Huntington's disease patients, polyglutaminated-huntingtin expression induces in Knock-in adult mice an anxio-depressive phenotype, with an influence of sex. An interesting result shows up with an anxious behavior observed mainly in male mice, and a depressive-like behavior in female mice. The anxio-depressive phenotype is much important than motor symptoms at studied ages. Expression of the modified huntingtin does not disrupt BDNF expression in adult hippocampus, but reduces two neurogenesis steps: proliferation and neuron maturation.

MODAFINIL SENSITIZES TO PSYCHOSTIMULATORY EFFECTS ON LOCOMOTION AFTER REPEATED ADMINISTRATION IN MICE

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The effects of a wakefulness promoting drug modafinil are quite similar to the effects of stimulants as methylphenidate and amphetamines. However, undesired effects such as hypersomnolence rebound, tolerance and dependence are absent. For this reason, modafinil is used not only for medical indications, but also to alleviate the sleep deprivation and fatigue in healthy population.

In many neuroactive substances with addictive potential, repeated administration leads to a progressively enhanced response-sensitization. The purpose of presented study was to evaluate development of behavioural sensitization to stimulatory effects on mouse locomotor activity in the open-field test after repeated administration of modafinil.

Adult male mice allocated into 4 groups were administered saline intraperitoneally (Groups 1, 3) and modafinil 10 mg/kg (Group 2) or 25 mg/kg (Group 4) in 7 daily doses. On the Days 8 and 14, challenge doses of modafinil were given to all animals (10 mg/kg in Groups 1, 2; 25 mg/kg in Groups 3, 4). Open-field activity was recorded on the Days 1, 8 and 14.

Acute administration of modafinil caused increase of locomotion and rearing at both doses tested. Stimulatory effects of modafinil on locomotion and rearing were increased in mice after repeated pre-treatment (Groups 2 and 4) compared to animals challenged by the first dose of modafinil on the Day 8 (Groups 1 and 3) and on the Day 14 (Group 4) compared to challenge doses in control animals.

Repeated administration of modafinil leads to development of behavioural sensitization to psychostimulatory effects on both horizontal and vertical locomotor activities in mice. Despite of a safe modafinil profile reported, repeated use of this drug can perhaps cause certain neuronal plastic changes in circuitry mediating modafinil-induced stimulation and thus massive usage of modafinil for non-medical reasons might have unpredictable consequences.

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A MOUSE MODEL OF SLEEP DISTURBANCES AND HYPERAROUSAL IN POST-TRAUMATIC STRESS DISORDER (PTSD): THE ROLE OF CUE REMINDERS IN THE TRAUMA-RELATED DEFICITS

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Animal models of post-traumatic stress disorder (PTSD) have been developed, but they address a limited range of behavioral or physiological parameters following stress, such as anxiety, cognition, elevated cortiscosterone levels. Among the long-term consequences of traumatic stress exposure is a profound alteration in sleep quality, a phenomenon, which has been poorly studied yet. Therefore, the objective of the present study was to investigate the short (24 h post-stress)- and long-term (7, 14 or 21 days post-stress) effects of an acute severe stress on sleep/wakefulness in mice, using a cue reminder, e.g. an object that was present during shock exposure.

Swiss mice were implanted with electrodes for transcranial electroencephalographic (EEG) recording of sleep/wakefulness cycles during their light period. Two weeks after surgery, baseline EEG recording, measuring sleep parameters (NREM sleep and wakefulness) was performed in a neutral context (similar to their homecage), to which mice had been habituated. Two days later they were subjected to two unavoidable electric foot-shocks in the presence of an object. One, 7, 14 and 21 days later, animals were exposed to the same context, with or without the object previously paired with the shock for 5 min, and EEG recording was performed for 6 h thereafter.

Results showed that at day 1, 7, 14 and 21 post-stress, mice, which were exposed or not to an object, displayed a profound alteration of the sleep architecture, consisting of a greater fragmentation of sleep periods. Moreover, in animals exposed to an object, total duration of wakefulness over 6 h was significantly increased at days 7, 14 and 21 post-stress.

In conclusion, these findings demonstrate for the first time that an acute severe stress may cause long-lasting alterations in sleep patterns. Such modifications may be reminiscent of the profound changes in sleep quality observed in patients suffering from PTSD, and therefore this model may be useful for the understanding of the mechanisms involved in this condition and for the identification of potential drug treatments.

BEHAVIORAL PHARMACOLOGY OF THE PSYCHEDELIC 4-BROMO-2,5-DIMETHOXYPHENYLETHYLAMINE (2C-B)

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4-bromo-2,5-dimethoxyphenylethylamine (2C-B, Nexus) is a hallucinogenic drug frequently abused as an ecstasy substitute. Although a well known recreational drug, the behavioral pharmacology of the compound is not well understood. The effects of serotonin 5-HT2A/C, noradrenergic α1/2, dopamine D2 antagonists, and serotonin and noradrenaline reuptake inhibitors on 2C-B's behavioral profile were examined. Changes in dopamine release in nucleus accumbens in rats were also studied.

Locomotor effects in the open field and deficits in the test of prepulse inhibition (PPI) of acoustic startle reaction (ASR) induced by 2C-B 10 and 50 mg/kg 60 min after subcutaneous (s.c.) administration were studied under the presence of either MDL-100907, SB-242084, prazosin, idazoxan, citalopram, desipramin or haloperidol. Dopamine levels in nucleus accumbens after subcutaneous administration of 2C-B 25 mg/kg were measured via a microdialysis for 4 h. The levels of dopamine and its metabolites homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine (3-MT) were analyzed with gas chromatography-mass spectrometry (GC-MS).

Locomotion was slightly increased and PPI was disrupted after 2C-B treatment. Effects were slightly potentiated by 5-HT2C antagonist, 5-HT2A, D2 and partly α1/2 antagonists blocked locomotor effects. Whereas the disruption of PPI was restored by antagonists of the 5-HT2A and D2 receptors, no effect was observed after the 5-HT2C antagonism. Neither citalopram nor desipramine affected any of the parameters analyzed. Finally, 2C-B 25 mg/kg significantly increased dopamine levels in nucleus accumbens to approximately 300% (3 pg/10 µl) of the baseline. The metabolites HVA and 3-MT were also increased, while DOPAC was decreased.

To conclude serotonergic, noradrenergic as well as dopaminergic receptors influence 2C-B's behavioral profile. The increase of dopamine in nucleus accumbens reflects the possible addictive potential of the compound.

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SUSTAINED TREATMENT WITH THE MONOAMINE TRANSPORTER INHIBITORS DULOXETINE AND DOV-216,303 INCREASES RODENT BDNF PROTEIN LEVELS IN VITRO AND IN VIVO

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The neurotrophic hypothesis for depression assumes that drugs optimized to restore brain derived neurotrophic factor (BDNF) levels in brain areas vulnerable to the effects of stress such as the hippocampus, consist of a novel class of antidepressants. Serotonin reuptake inhibitors (SSRIs) and dual serotonin and noradrenaline transporter reuptake inhibitors (SNRIs) increase brain BDNF levels. Recently 'triple' serotonin, noradrenaline and dopamine inhibitors have been discovered that may possess a different neurogenic profile than single or dual inhibitors. We tested the effects of the putative triple inhibitor, DOV-216 313 (1–100 µmol/l), on BDNF protein levels in mouse hippocampal neuronal HT22 cells and in rat C62B astrocytoma cells. In addition, rats were treated for 21 days with DOV-216 303 (30 mg/kg/day, i.p.) and BDNF protein levels were determined in the hippocampus and prefrontal cortex. The effects of DOV-216,303 were compared with those of the SNRI duloxetine (1–50 µmol/l and 30 mg/kg/day, i.p.). BDNF protein levels were determined by ELISA. Both compounds increased intracellular BDNF protein levels in the astrocytoma cells. DOV-216 303 increased intracellular BDNF in the neuronal cells, whereas there was only a tendency for an increase for duloxetine. Injection stress alone caused a more marked decrease in hippocampal than prefrontal BDNF. The reduction in BDNF in the hippocampus was reversed by both compounds, whereas only DOV-216 303 induced a small increase in prefrontal BDNF. These data provide a first hint towards a potentially more robust BDNF increasing effect for DOV-216 313. Future studies should determine to what extent the neurotrophic profile for this novel class of drugs indeed differentiates from the profile of SSRIs and SNRIs, and if this translates into a differentiated, and potentially superior, antidepressant profile.

CYCLOSPORINE A ATTENUATES 3-NITROPROPIONIC ACID INDUCED HUNTINGTON'S LIKE SYMPTOMS IN RAT: POSSIBLE NITRIC OXIDE MECHANISM

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Role of oxidative stress has been well known in neurodegenerative disorders. 3-nitropropionic acid (3-NP), plant based mycotoxin that produce HD like symptoms in animals. Oxidative stress and nitric oxide mechanisms have been recently proposed in the 3-NP induced neurotoxicity. Cyclosporine A is a well-known immunosuppressant drug that is presently used for prevention of allograft rejection. The present study was conducted to explore the therapeutic potential of cyclosporine A against 3-nitropropionic acid-induced neurotoxicity, an animal model of Huntington's disease. Systemic administration of 3-NP (10 mg/kg) for 14 days significantly impaired body weight, motor activity, biochemical parameters (raised lipid peroxidation, nitrite concentration, depletion of superoxide dismutase and catalase) and mitochondrial enzymes. Cyclosporine A (2.5, 5 and 10 mg/kg) treatment significantly attenuated behavioral, biochemical and cellular alterations. Further, L-arginine pretreatment with cyclosporine A (5 mg/kg) significantly reversed the protective effect of cyclosporine A. However, L-NAME (L-Nitro-Arginine Methyl Ester) (10 mg/kg) pretreatment potentiated the protective effect of cyclosporine A (5 mg/kg). Study highlights the therapeutic potential of cyclosporine A in the treatment of Huntington's disease. Study suggest that nitric oxide modulation in involved in the neuroprotective effect of cyclosporine A against 3-NP neurotoxicity.

CANNABINOID-INDUCED MODULATION OF BEHAVIOURAL STEREOTYPIES INDUCED BY AMPHETAMINE IN A PUTATIVE MOUSE MODEL OF AUTISM

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Stereotyped behavioural syndrome represents one core symptom of major neuropsychiatric disorders, such as schizophrenia and autism-spectrum disorders (ASD). In animal models, compulsive behaviour can be elicited by high-dosage amphetamine administration. The exposure to psychostimulants has been shown to affect hippocampal neurogenesis and increase spines density in the nucleus accumbens. One aim of this study was to investigate the behavioural response to d-amphetamine

(10 mg/kg, i.p.) challenge in wild-type (wt) and heterozygous (rl/+) reeler male mice (strain B6C3Fe a/a−), a putative model of ASD. Mutant mice have been shown altered density of D2 and D3 receptors in the striatum area. Different profiles emerged as a function of genotype in the stimulated crossing and rearing behaviours. The stereotyped sniffing and licking/gnawing activities induced by the psychostimulant were also more marked in rl/+ mice compared to wt littermates. Genotype by drug interaction was also assessed for plasticity-related parameters in brain areas. Recent work reports a modulation exerted by cannabinoid agents on stereotyped behaviour in Parkinson's disease models. Thus, we were interested in assessing these modulatory effects in our model. To this aim, the indirect cannabinoid agonist, know to inhibit anandamide hydrolysis (URB, 0 or 0.3 mg/kg, i.p.) was administered i.p. 30 min before d-amphetamine challenge. The administration of URB efficaciously contrasted in wt mice the expression of compulsive sniffing, and thus increased the involvement in locomotor activity. In contrast, for the rl/+ mice, the administration of URB was less able to reduce the involvement in amphetamine-induced compulsive behaviour and locomotor hyperactivity. These findings indicate that a more marked stereotyped behavioural syndrome is elicited by amphetamine in our ASD mouse model. Stimulation of CNS cannabinoid system seems to represent a suitable tool for therapeutic modulation of exacerbated motor symptomatology characterizing major neuropsychiatric developmental disorders.

ACUTE METHAMPHETAMINE INDUCES DIFFERENT BEHAVIOR IN ELEVATED PLUS MAZE AND SOCIAL INTERACTION TEST IN RATS

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Psychostimulants have been shown to affect human behaviour in serious manner; specifically they induce aggressive behaviours and impair social interaction. Increased anxiety caused by psychostimulants was found in several types of tests. The aim of the present study was to assess the effect of low dose of methamphetamine (MA) on anxiety in adult male and female rats. Test of social interaction (SIT) and elevated plus maze test (EPM) were used to test anxiety. In females the phase of estrous cycle (proestrus/estrus, diestrus) was determined before testing. 1 mg/kg MA or saline were administered subcutaneously 30 min prior to testing. For the SIT the behaviour of two foreign animals of the same sex/estrous phase and treatment was recorded for 5 min in an Open field arena. Duration and frequency of social and non-social activities were evaluated. In the EPM test one animal was placed in the centre of the apparatus and its behaviour was recorded for 5 min. Time spent in open arms, closed arms, frequency of stretched-attend posture, locomotion and rearing were evaluated. Our results showed that acute dose of MA decreased social interaction in both sexes. On the other hand, in both males and females MA increased time spent in open arms and decreased time spent in closed arms. Locomotion and rearing in the EPM were not altered by acute MA application. These results indicate that anxiety was increased in the SIT but decreased in the EPM after acute dose of MA. Thus, in the present study we demonstrated that while acute MA decreases anxiety to heights and novel environment, it increases anxiety to a foreign animal.

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THE EFFECT OF ESTROGEN ON SENSORIMOTOR PROCESSING IN MDMA-TREATED OVARIECTOMIZED FEMALE RATS

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3,4-Methylenedioxymethamphetamine (MDMA), an illicit designer drug with significant abuse potential, increases release of serotonin and inhibits serotonin transport (SERT). It has been suggested that estrogen influences the effect of MDMA through its effect on the serotonin-1A receptor and SERT. The goal of our study was to measure the influence of estrogen on the effect of MDMA on sensorimotor processing. Sensorimotor processing is typically disrupted by compounds active in the serotonergic system and is measured by the test of prepulse inhibition (PPI) of acoustic startle reaction.

Female Wistar rats were ovariectomized (OVX); one week after the surgery they received 10 µg/0.2 ml s.c. 17β-estradiol dissolved in oil 46–48 h before the experiment. MDMA (2.5 or 5 mg/kg s.c.) was applied acutely 15 min before the experiment. We measured PPI and level of estrogen in plasma samples.

We found elevated levels of estrogen after hormonal substitution from 20 to 80 pg/ml. Estrogen disrupted PPI in control rats but not in MDMA-treated rats. We found that estrogen blocked the effect of MDMA on PPI. This result corresponds to our previous work which demonstrated that the effect of MDMA was disrupted in female rats in proestrous-estrous phase with elevated levels of estrogen (Bubenikova *et al.*, 2005).

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