



THE 3RD FINNISH SYMPOSIUM
ON BIOLOGICAL PSYCHIATRY

PSYCHIATRIA FENNICA

Supplementum 1, 2018

THE 3RD FINNISH SYMPOSIUM ON BIOLOGICAL PSYCHIATRY

ABSTRACT BOOKLET

Psychiatria Fennica 2018, vol. 49, Suppl. 1
Foundation for Psychiatric Research Publication Series

ISSN 2489-6152

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First printing

Publisher Foundation for Psychiatric Research
Address Fredrikinkatu 71 A 4
FI-00100 Helsinki
FINLAND

Telephone +358 50 5125292

Cover design S.-O. Westerlund

Helsinki 2018

PSYCHIATRIA FENNICA

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December 19, 2017

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* Abstract will also be presented as a short talk

Interhemispheric connectivity of the human brain: the effect of prenatal exposure to maternal cigarette smoking

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Corpus callosum (CC) is the main interhemispheric fiber tract in the human brain, consisting of about 200 million axons. Heterogeneity of its fiber composition suggests that cortical regions differ in the type of channels carrying information between their left-right homologues. Mutually connected cortical regions and the respective callosal fibers together present modules of interhemispheric information transfer that are affected by numerous pathological and developmental factors including prenatal exposure to maternal cigarette smoking (PEMCS). We modeled interhemispheric connectivity using diffusion tractography in a sample of 100 unrelated individuals from the Human Connectome Project. Those pairs of cortical regions and the callosal segments through which they are most consistently connected were included to form 6 modules. Then we assessed the similarity in structural values in each of the 6 callosal segments (MTR) and 16 cortical regions (MTR and cortical thickness), as well as their inter relationship in 450 young adults from the Northern Finland Birth Cohort 1986. Callosal MTR correlated consistently with cortical MTR in all modules. Cortical MTR was found to be negatively correlated with cortical thickness in all but one cortical region, namely the precentral gyrus, primarily connected through the posterior part of the callosal body. This cortical site is also the only one to show significantly stronger effect in the correlation between cortical MTR and cortical thickness in those exposed prenatally to maternal cigarette smoking. We speculate such a stronger correlation in this group may reflect greater variability in dendritic arborization.

Neonatal regulatory behavior problems are predicted by maternal early pregnancy overweight and obesity: findings from the prospective PREDO Study

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Introduction

Maternal overweight/obesity and co-morbid hypertensive disorders and GDM have been linked with neurodevelopmental delay in the offspring in childhood. We hypothesized that these maternal conditions associate with early signs of neurodevelopmental adversity, namely infant regulatory behavior problems, and that infant regulatory behavior problems mediate the link between maternal conditions and child neurodevelopment.

Methods

3117 women of the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction Study filled in the Neonatal Perception Inventory at the infant's mean age of 16.9 (SD=7.6) days and 2116 of them the Ages and Stages Questionnaire at the child's mean age of 42.2 (SD=8.3) months. Data on maternal BMI, chronic and gestational hypertension, pre-eclampsia and GDM were extracted from the Finnish Medical Birth Register.

Results

Infants of overweight/obese mothers in comparison to infants of normal weight mothers had higher levels of regulatory behavior problems and 22% (95% CI 5-42%) higher odds of having problems in multiple domains of behavioral regulation. These effects were not confounded by the co-morbid disorders. Regulatory problems in infancy partially mediated the association between maternal overweight/obesity and childhood developmental milestones. Co-morbid hypertensive disorders and GDM did not associate with infant regulatory behavior problems and did not add to the effects of overweight/obesity.

Conclusion

Our findings suggest that regulatory behavior problems in infancy, especially multiple regulatory problems predictive of later neurodevelopmental adversity, have prenatal origins that can be partly attributed to maternal overweight/obesity. Decreasing the rates of overweight/obesity in women of childbearing age will improve the neurodevelopment of their offspring.

Chemogenetic manipulation of nucleus accumbens and insula activity alters alcohol consumption in alcohol-preferring rats

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The nucleus accumbens (NAc) is a key structure involved in mediating motivational and emotional processes, whereas the insular cortex (INS) is implicated in interoceptive effects and decision making during goal-directed actions. Neuroimaging studies have shown that both are activated during voluntary alcohol drinking in rats. To examine their role in the regulation of alcohol drinking, we used viral-mediated gene transfer of designer receptors exclusively activated by designer drugs (DREADDs) to either activate (Gq-DREADD, AAV8-hSyn1-hM3D(Gq)-mCherry) or inhibit (Gi-DREADD, AAV8-hSyn1-hM4D(Gi)-mCherry) NAc and INS neurons. We trained alcohol-preferring AA (Alko, Alcohol) rats to drink 10% alcohol during 2-h sessions every second day offering tap water as the alternative. Once stable baseline drinking was established, we microinjected the DREADDs bilaterally into the NAc or anterior INS. Following a four-week DREADD expression, we activated DREADDs with clozapine-N-oxide (10 mg/kg, ip). After conclusion of the experiments, DREADD expression was verified from coronal brain sections by immunohistochemistry. Silencing of the NAc with the Gi-DREADD significantly decreased alcohol drinking, whereas activation with the Gq-DREADD increased alcohol intake while also affecting water consumption. No significant effects on alcohol drinking were seen in the control group (control vector: AAV8-hSyn1-EGFP). In contrast, the activation of the INS with the Gq-DREADD significantly decreased alcohol drinking. The Gi-DREADD and control groups displayed no changes in intake. The results show that NAc and INS belong to the forebrain neurocircuitry underlying alcohol reinforcement and consumption. The differential effects produced by activity manipulation in these brain areas suggest that they have diverse functions in controlling alcohol drinking.

Brain region-specific alterations in myelination after chronic psychosocial stress in mice

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Chronic psychosocial stress is a major risk factor for anxiety disorders and depression. The molecular mechanisms underlying stress susceptibility and resilience are largely unknown. The chronic social defeat stress (CSDS) mouse model predisposes mice to anxiety-like behavior. Mice undergo 10 days of defeat during which they are confronted by an aggressor mouse. As mice become defeated some show anxiety-like behavior (susceptible) whereas others do not (resilient). We used two inbred mouse strains, C57BL/6CrJ (B6) and DBA/2CrJ (D2), expecting genetic background to considerably impact the response. We have previously shown that myelin-related genes are differentially expressed in defeated mice in the ventral hippocampus (vHP), bed nucleus of the stria terminalis (BNST) and prefrontal cortex (pFC), all previously associated to anxiety disorders. Myelin is produced by oligodendrocytes (OLGs). To examine whether the number of OLGs or the amount of myelin is affected after CSDS, we used immunohistochemical staining of CNPase (OLGs) and BlackGold II (myelin). In the BNST, B6 resilient mice had more OLGs after CSDS compared to the susceptible mice. Differences were not observed in other brain regions or in D2 mice. The size of the myelinated area did not differ between defeated and control mice. Furthermore, there was no correlation between the number of OLGs and the myelinated area. To investigate if stress affects major white matter tracts, we measured the thickness of the corpus callosum, which did not differ between defeated and control mice. Our findings suggest possible region and genetic background-specific dynamic myelin plasticity after CSDS.

Chronic psychosocial stress in mice alters brain myelination in a genetic background-dependent manner

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Chronic psychosocial stress is a well-established risk factor for psychiatric disorders, but the mechanisms by which stress impacts susceptibility are largely unknown. The chronic social defeat stress (CSDS) mouse model allows identifying factors underlying resilience and susceptibility to chronic psychosocial stress. It involves daily 5-10 minute confrontations of two conspecific male mice repeated for 10 days. We used this model and RNA-seq to identify biological pathways affected by CSDS in three brain regions: medial prefrontal cortex (mPFC), ventral hippocampus (vHPC), and bed nucleus of stria terminalis (BNST). Since we expected genetic background to influence the response to CSDS, we used two inbred mouse strains: C57BL/6CrI (B6) and DBA/2CrI (D2). The strains showed distinct behavioral responses: 69 % of B6 but only 5% of D2 mice were resilient to stress. We discovered with RNA-seq that differential expression of oligodendrocyte-related genes was over-represented in gene-set enrichment analysis of all studied brain regions. Because oligodendrocytes affect CNS function primarily by myelinating axons, we used TEM to establish that B6 stress-resilient mice had thicker myelin of small mPFC axons compared to controls. In the vHPC, susceptible B6 mice had thinner myelin, while in the BNST they had thicker myelin, compared to controls. D2 resilient mice had thinner myelin in mPFC axons compared to susceptible mice. Corpus callosum thickness did not differ between stressed and control animals as measured by IHC, suggesting that stress effects on myelination are regionally selective. Our findings suggest possible genetic background-dependent white matter plasticity in response to CSDS in mice.

Intergenerational transmission of substance abuse: A genetically informed population study

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Parental substance abuse (SA) is associated with elevated risks for substance use problems and antisocial behavior in the offspring but mechanisms underlying the intergenerational associations remain unclear. To estimate the contribution of genetic and non-genetic factors, we conducted children-of-siblings analyses in a population-based sample of offspring of monozygotic and dizygotic twin, full sibling, and half-sibling parents. Parental SA was identified from Swedish nationwide medical and legal registries as diagnoses of alcohol/drug use disorders and alcohol/drug related criminal convictions, and offspring outcomes came from the same sources. In individual-level analyses among nearly 2.5 million offspring (born 1958-1995), both maternal and paternal SA more than doubled the risk for SA (maternal hazard ratio [HR]=2.81 [95% CI: 2.77-2.86]; paternal HR=2.51 [2.49-2.54]) and criminality (maternal HR=2.20 [2.17-2.23]; paternal HR=2.07 [2.05-2.09]) in the offspring. Structural equation models were used to estimate the proportions of variance and covariance due to genetic and environmental factors for parental SA and the offspring outcomes. Additive genetic effects explained 42% (95% CI: 28-56%) and 46% (36-55%) of the variance in maternal and paternal SA, respectively, and between 37% (31-44%) and 53% (47-58%) of the variance in the offspring outcomes. Only additive genetic effects significantly contributed to the intergenerational associations between paternal SA and the offspring outcomes as well as maternal SA and offspring criminality. In contrast, the association between maternal and offspring SA was due to genetic (54% [95% CI: 25-84%]), extended family environmental (17% [2-31%]) and nuclear family environmental (29% [12-45%]) factors, suggesting also potential environmental transmission.

Early adversity, polygenic risk score for schizophrenia and brain response to faces

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Early life adversities shape the human brain during childhood and adolescence and might influence the interindividual differences in vulnerability to schizophrenia - probably in part via glucocorticoid system. In our previous study we discovered that early adversities associate with brain response to faces and that this association varies as a function of the expression levels of the glucocorticoid receptor gene (data from Allen Human Brain Atlas) (Lieslehto et al., 2017). Here we explore whether early adversities modulate the association between polygenic risk score for schizophrenia (PRS) on both functional and structural covariance within the face-processing network. A total of 90 individuals (mean age 21) drawn from the Northern Finland Birth Cohort 1986 (both functional and structural data available) were used for discovery analyses and 126 individuals (mean age 26) with only structural data available were used for replication analyses. Trauma And Distress Scale (TADS) was used to map retrospectively the level of early adversity in each individual. High-adversity group (TADS scores above median) displayed lower functional and structural covariances as a function of PRS. Similar phenomenon was detected in our replication sample (structural covariance). We speculate that early adversities modulate the link between PRS and face processing network possibly via hypothalamus-pituitary-adrenal (HPA) axis.

NETO2 regulates fear expression in mice

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Ionotropic glutamate receptors [AMPA, NMDA and kainate receptors (KARs)] mediate excitatory neurotransmission in the brain. KARs have been implicated in psychiatric disorders in humans, and in anxiety-like behavior in mice. Their function is finely modulated by auxiliary subunits, the NETO proteins (NETO1 and NETO2). We hypothesized that these proteins may regulate anxiety through modulation of KARs. We tested this hypothesis by carrying out a comprehensive behavioral analysis of Neto1 and Neto2 knockout (KO) and wild-type (WT) mice, both males and females that were 8 weeks old at the beginning of the behavioral testing. We did not observe differences between the genotypes in anxiety tests based on approach-avoidance conflict (elevated plus maze, elevated zero maze, light/dark box and open field tests) or in home cage locomotor activity. In cued fear conditioning Neto2, but not Neto1, KO mice showed higher fear expression and delayed extinction compared to the WT mice. In addition, we determined Neto2 expression pattern using fluorescent in situ hybridization to identify the cell types that express it. Our results show that Neto2 is expressed in fear-related brain areas (i.e. medial prefrontal cortex, amygdala and hippocampus) in both excitatory and inhibitory neurons. In conclusion, our results demonstrate that Neto2 regulates fear expression and extinction in mice. Furthermore, it is widely expressed in fear-related brain regions, but the underlying physiological mechanisms remain to be determined.

Ketamine-induced network modulation in female and male rodent brain

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A dissociative anesthetic and an N-methyl-D-aspartate receptor (NMDA-R) blocker ketamine has recently received considerable attention as a rapid-acting antidepressant albeit the neurobiological basis for these intriguing effects remain unclear. Increased neuroplasticity through activation of brain-derived neurotrophic factor (BDNF) receptor tropomyosin-related kinase B (TrkB) and inhibition of glycogen synthase kinase 3² (GSK3²) are among the suggested mechanisms. We have here investigated the electroencephalogram (EEG) responses and changes in the aforementioned molecular-level events in adult rodents as a response to single subanesthetic doses (10-50 mg/kg) of ketamine. Ketamine dose-dependently inhibited GSK3² and increased both gamma oscillations (25-100 Hz) and TrkB signaling, with the highest dose 50 mg/kg producing the most prominent changes. Interestingly, the EEG power increase differed between female and male animals at lower gamma frequencies (25-40 Hz) in response to ketamine. This led us to investigate ketamine-induced effects and their potential difference between genders in brain network level using functional magnetic resonance imaging (fMRI). Specifically, we measured the resting-state (RS) functional connectivity 24 hours after a single ketamine injection (50 mg/kg) in female and male rats. Suppressed RS functional connectivity was observed in several brain regions in ketamine-treated animals compared to controls. Significant interactions between ketamine treatment and gender were also observed, indicating ketamine's ability to modulate functional connectivity differently in female and male brain. These observations unveil important aspects of neurobiological brain responses to ketamine and emphasize the importance of gender factors in these responses.

Association between smoking and depression: a longitudinal investigation among twins from late adolescence to young adulthood

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Introduction: Longitudinal research is needed to understand the relationship between cigarette smoking and depressive symptoms. Our aim was to examine the bi-directional association between cigarette smoking and depressive symptoms from adolescence to young adulthood. Materials and methods: We analyzed prospective longitudinal data from twins participating in the adolescent (mean age 17.5) and young adult (mean age 22) surveys of the FinnTwin12 study (N=2,954). Both smoking patterns and depressive symptoms were assessed. Depressive symptoms were assessed with the 10-item version of the General Behavior Inventory. We used negative binomial regression and multinomial logistic regression analyses, further adjusted for multiple confounders. Additionally, we conducted within pair analyses to control for familial confounding. Results: Cigarette smoking during adolescence predicted depressive symptoms in adulthood. The Incidence Rate Ratio (IRR) estimates, when adjusted, were higher among daily smokers (IRR=1.17, 95% CI 1.02- 1.34) compared to never smokers. Conversely, having higher depression scores in adolescence were associated with an increased risk of becoming a non-daily and daily smoker later. In the within-pair analysis for smoking predicting depression, the results were attenuated compared to the individual analysis, suggesting shared familial confounding (Ever smokers: IRR 1.11 95% CI 0.99-1.24). Also, for depression predicting smoking, the results suggested possible shared familial confounding. Conclusions: Cigarette smoking during adolescence is a significant predictor of depressive symptoms later in life. Additionally, depressive symptoms during adolescence are associated with an increased likelihood of becoming a smoker. However, the associations may not be independent of measured confounding factors and shared familial influences.

Bradykinin receptor B2 in anxiety

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Bradykinin is an endogenous nonameric peptide derived from kininogen. It has several central and peripheral effects that are mediated by bradykinin receptor B2 (BDKRB2). In mice, intracerebroventricularly injected bradykinin has anxiogenic effects whereas intra-periaqueductal grey matter injected bradykinin attenuates panic reaction. Genetic variation within human BDKRB2 gene may associate with panic disorder. Here we studied the role of kininogen and BDKRB2 in mouse stress and anxiety-like behavior. We tested the effect of BDKRB2 antagonism and agonism on mouse behavior, and analysed the expression of BDKRB2 in brain and kininogen in brown adipose tissue of stressed mice. Subcutaneously injected antagonists induced anxiolytic effect in the open field test of DBA/2J mice. Antagonists did not have anxiolytic effect in the light dark, elevated plus maze or novelty suppressed feeding tests. Further, intraperitoneally injected antagonists were without anxiolytic effect in the open field test of DBA/2J and C57BL/6J mice. Intraperitoneally injected BDKRB2 peptide agonist reduced locomotor activity in the open field test of C57BL/6J mice and increased immobility time in forced swim test of DBA/2J mice. Restraint stress (2h + 1h recovery) downregulated BDKRB2 protein expression in hippocampus and cold stress (4 °C for 4h) upregulated kininogen gene expression in brown adipose tissue of C57BL/6J mice. BDKRB2 antagonism in DBA/2N mice had antipyretic effect and reduced stress-induced hyperthermia. In conclusion, pharmacological inhibition of mouse BDKRB2 had anxiolytic effect whereas BDKRB2 activation had a pro-depressant effect. Bradykinin precursor was upregulated in brown adipose tissue by cold stress, and BDKRB2 antagonist reduced body temperature in mice. Our results suggests that BDKRB2 mediates stress responses and thermoregulation in mice.

Dual-task training reduces distractor-related brain activation in a lifelike situation in ADHD

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Individuals with attention deficit hyperactivity disorder (ADHD) have difficulties both in updating incoming information in working memory, and in suppressing irrelevant information. There is evidence that working memory training may bring some amelioration to attention control deficits reflected in everyday life as inattention and distractibility. However, the neuronal mechanisms underlying working memory training effects in ADHD are unclear and we do not know which processes mediate reduction of symptoms. We conducted a series of fMRI experiments to clarify these issues. A total of 53 individuals with ADHD and 30 healthy controls participated in experiments in which their brain activity was measured during 1) n-back working memory updating tasks, and 2) when they watched a film depicting lifelike 'cocktail party' environment with various ambient noises. As compared with the healthy controls, the ADHD participants showed decreased activity in working memory updating tasks and increased sensory activation, as well as higher sensitivity to ambient noises when viewing social interaction. Thirty-eight individuals with ADHD further participated to dual task training study for 5 weeks. Half of them were randomly allocated to a training group practicing visuospatial-phonological dual tasks, and the other half to an active control group playing a video game. The dual task training group showed increased task-related activity associated with updating, and decreased noise-related activity during film viewing at the post test following training. Our findings suggest that training-related up-regulation of top-down attentional control systems reduces distractor-related activity and could be a mechanism mediating improvements in measures related to everyday life.

Arginine vasopressin activates hippocampal interneurons to suppress neuronal network activity during birth: implications for neuroprotection

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During birth, a number of homeostatic and pre-adaptive mechanisms involving cardiovascular and respiratory systems are activated in mammals to promote survival of the neonate during the abrupt transition to extrauterine life. Most of these effects are triggered by a profound stress-hormone response involving the sympathetic nervous system and the HPA axis, including a massive release of arginine vasopressin (AVP) from the pituitary into the blood. However, there is no information on whether this peripheral vasopressinergic surge is paralleled by AVP signalling arising from central (hypothalamic) sources, acting directly upon vulnerable neuronal networks in the perinatal brain. By utilizing CLARITY optimized light-sheet microscopy in rat brains, we discovered that vasopressinergic fibers innervate the neonate rat hippocampus. In order to study the putative effects of AVP on neuronal activity in the perinatal hippocampus, we performed *in vitro* electrophysiological experiments on hippocampal slices and intact hippocampi throughout the perinatal period (E21-P2) in rats and newborn (P0-2) guinea pigs. Exogenously applied AVP (10 nM) produced a strong suppression of network events in the hippocampal CA3 area, which was prevented by the V1a receptor antagonist SR 49059 (20-30 nM). Intracellular recordings revealed that AVP triggered tonic activation of stratum lucidum-radiatum interneurons. The sustained interneuronal activity caused a loss of synchronous GABAergic signalling, readily explaining the suppression of hippocampal network events. Thus, we suggest that AVP-mediated signalling within the brain exerts neuroprotective actions by reducing energy consumption, and prevents pathophysiological plasticity, by suppressing neuronal network activity during birth. These conclusions have several important consequences regarding the lifelong effects of complicated birth on brain development, especially in light of data showing that AVP release is further enhanced during birth asphyxia.

Work was published in PNAS in November 2017: <http://www.pnas.org/content/114/50/E10819.full>
doi: 10.1073/pnas.1717337114

Comparison of two mouse strains and brain regions in gene expression response to chronic stress

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We used the chronic social defeat stress (CSDS) model to investigate gene expression changes associated with anxiety-like behavior in two mouse strains, C57BL/6NCrI (B6), and DBA/2NCrI (D2). The two strains differ in their innate and stress-induced anxiety levels, B6 mice being largely resilient and D2 susceptible to stress. After CSDS mice were classified as resilient or susceptible based on the social avoidance test. We carried out RNA-sequencing (RNA-seq) and microRNA-sequencing (miRNA-seq) of medial prefrontal cortex (mPFC) and ventral hippocampus (vHPC) from resilient, susceptible, and control mice, sampled one week after CSDS. Differentially expressed (DE) genes were identified using limma. We used Rank Rank Hypergeometric Overlap (RRHO) tests to compare transcriptomic responses of susceptible and resilient phenotypes to CSDS. Weighted Gene Co-expression Network Analysis (WGCNA) was used to detect genes and miRNAs associated with stress, and the resulting gene modules were analyzed for enriched GO terms and pathways. B6 and D2 mice differ greatly in their CSDS-responding genes in the mPFC but showed highly shared gene expression changes in the vHPC. Of the 15 and 10 co-expressed gene modules associated with interaction of strain*stress in mPFC and vHPC, respectively, 14 (56%) were significantly conserved between brain regions (all Bonferroni $p < 0.05$). Most significantly enriched GO terms of the conserved modules included chemical synaptic transmission, cell adhesion, cell-cell signaling, synapse assembly, piRNA metabolic process, response to peptide hormone, and myelination.

Behavioral flexibility is improved by chronic fluoxetine treatment through BDNF/TrkB signaling

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Brain-derived neurotrophic factor (BDNF) is a major regulator of neuronal plasticity through the activation of its receptor tyrosine kinase TrkB. We have demonstrated that chronic fluoxetine treatment combined with fear extinction or monocular deprivation, but neither treatment alone, induced an enduring loss of conditioned fear memory or shift of ocular dominance in the visual cortex, respectively, activated by BDNF/TrkB pathway (Vetencourt et al., 2008; Karpova et al., 2011). Thus, chronic antidepressant drug treatment induces a critical period-like plasticity, which allows brain networks to better adapt to the internal and external milieu in the adult brain. However it is not clear whether spatial reversal learning or behavioral flexibility is improved by chronic fluoxetine treatment during learning process via BDNF/TrkB pathway. Here we used BDNF heterozygous knockout (*Bdnf* hKO) and heterozygous TrkB knockout specifically in Parvalbumin (PV)-expressing interneurons (hPV-TrkB) mice, and assessed the effects of fluoxetine on plasticity using IntelliCage (NewBehavior AG, Zurich, Switzerland), where transponder-implanted female mice were group-housed in a genotype-mixed manner. In IntelliCage water-deprived mice were rewarded by access to water when visiting conditioning corners in defined sequence during the acquisition phase, and then it was exchanged to the opposite direction in the reversal phase. In wild-type mice, chronic treatment with fluoxetine did not affect acquisition of the spatial memory but improved reversal learning. *Bdnf* hKO mice showed impaired acquisition of spatial memory as previously indicated (Linnarsson et al., 1997), but the treatment improved spatial memory in the acquisition and reversal phase to similar level as in the wild-type mice. On the other hand, hPV-TrkB mice showed slightly deficits in learning/memory in the acquisition and reversal phase, and the treatment with fluoxetine improved the impaired acquisition but not reversal learning. These results strongly suggest that fluoxetine promotes behavioral flexibility especially in the reversal learning task, by activating TrkB signaling in PV interneurons but BDNF-independent manner.

Ketone 3-hydroxybutyrate: a biomarker of aggression?

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Aggression is a complex behavior broadly involving many body systems, commonly investigated at the biological level within specific pathways. Studying metabolites in relation to aggression can shed light on the biology of aggression in a broader context of various biological pathways affecting behavior. Associations between metabolites and aggression are not well known. Here, using a selected set of 11 low molecular weight metabolites including amino acids and ketones, we aimed to identify metabolites that associate with adolescent aggression. Our dataset is a sub-sample of a population-based, longitudinal study of Finnish twins born in 1983-1987 with available plasma samples at age 22 and aggression levels rated in adolescence (N=725) by parents of the twins (at age 12), their teachers (at ages 12 & 14), or the twins and their co-twins (at ages 14 & 17). Linear regression models, adjusted for age, sex, body mass index and the clustered twin data, were used with the metabolite as the outcome and aggression levels as predictors. Five metabolites showed unadjusted correlations greater than 0.1 with aggression. However, we found that aggression showed consistent negative associations only with 3-hydroxybutyrate, a ketone body produced in the fasting state. Effect sizes for different single raters were generally similar in magnitude, while age 12 teacher-rated aggression and age 14 self-rated aggression were both significant predictors of 3-hydroxybutyrate in multi-rater modeling. These exploratory results indicate ketone metabolism as a possible new pathway to investigate further to better understand the biology of aggression.



Finnish Foundation for Psychiatric Research