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The role of the caudal linear nucleus in the circuitry underlying alcohol preference and consumption

Petri Hyytiä, Mateusz Dudek
University of Helsinki, Finland

Abstract

Alcoholism is a chronic, progressing, and relapsing psychiatric disorder with a substantial genetic background. The neural circuitry mediating alcohol reinforcement, seeking, and relapse has not been fully delineated. The aim of the present experiments was to acquire further insight into the neural systems associated with alcohol preference and high voluntary alcohol drinking in the alcohol-preferring AA (Alko Alcohol) rats by using both neuroimaging and pharmacological tools. First, we compared the basal brain activity of AA rats with that of heterogeneous Wistar rats with manganese-enhanced magnetic resonance imaging (MEMRI). For manganese administration, alcohol-naïve rats were implanted with subcutaneous osmotic minipumps delivering 120 mg/kg $MnCl_2$ over a 7-day period, and were then imaged with a three-dimensional rapid acquisition-relaxation enhanced pulse sequence. MEMRI image analysis revealed that the most conspicuous subcortical activation difference was located in the caudal linear nucleus of raphe (CLi), with AA rats displaying a significantly lower T1 signal in this region compared to Wistar rats. However, long-term alcohol drinking by AA rats restored the CLi activity. In the second experiment, the CLi was targeted with pharmacological tools. AA rats trained to drink 10% alcohol during 2-hour sessions were implanted with guide cannulas aimed at the CLi and given injections of the $GABA_A$ receptor agonist muscimol into the CLi before drinking sessions. Muscimol dose-dependently increased alcohol drinking, and co-administration of the $GABA_A$ antagonist bicuculline blocked muscimol's effect. These findings add to increasing evidence supporting the role of the mediocaudal VTA in the reinforcing actions of drugs of abuse. In particular, the present data suggest that the CLi is important for the propensity for high alcohol drinking and controls alcohol reward via GABAergic transmission.

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Altered temporo-striatal and fronto-cingulate circuits in acute methamphetamine nonhuman primate model

Jin-Young Kim[1], Ji-Won Chun[2], Jihye Choi[2], Han-Na Kim[3], Chang-Yeop Jeon[3,5], Kyu-Tae Chang[3,4], Sang-Rae Lee[3,4], Dai Jin Kim[2*]*
[1] Department of Biomedicine & Health Science, The catholic University of Korea College of Medicine, Seoul, South Korea [2] Department of Psychiatry, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea [3] National Primate Research Center (NPRC), Korea Research Institute of Bioscience and Biotechnology (KRIBB), Cheongju, Republic of Korea [4] Department of Functional Genomics, University of Science and Technology, Daejeon, Republic of Korea [5] Department of Biomedical Engineering, College of Medicine, Chungbuk National University, Cheongju, Republic of Korea
[*]correspondence: kdj922@catholic.ac.kr, srlee@kribb.re.kr

Abstract

Methamphetamine (MA) is strong central nervous system stimulant knowns, both in humans and in animals. However, there have been no previous studies which investigate brain alterations by period after injection in acute model. So this study aimed to estimate the alteration of the resting-state functional connectivity (rsFC) of the caudate nucleus(CN), anterior cingulate cortex (ACC), and superior frontal gyrus (SFG) as regions of interest(ROIs) after MA administration in none human primate.

16 macaca fascicularis (6months-11years) were evaluated once (baseline) before MA injection and 7 times (12hours-4weeks) after MA injection (2mg/kg, intra-muscle). The MRI data were acquired using a 3T MRI system (Philips Achiva), and the resting-state images were preprocessed and analyzed with the statistical parametric mapping toolbox (SPM8). To examine the changed rsFC of seeds, we used a seed-based correlation approach. Results were considered statistically significant if they exceeded the uncorrected $p < .005$ with an extent threshold of 10 voxels.

The rsFC from the left CN to the middle temporal gyrus was decreased steadily for period of 4 weeks after MA injection. In addition, from the left SFG to the ACC showed decreased rsFC in the same period. The observations of dysfunction of temporo-striatal and fronto-cingulate circuit in acute MA nonhuman primate model suggest that acute effect of MA induce functional abnormality in the brain.

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Neural Circuits for Stress-related Impulse Control Difficulties in Alcoholism

Dongju Seo[1], Cheryl Lacadie[2], and Rajita Sinha[1]
Departments of Psychiatry[1] and Radiology[2], Yale University School of Medicine

Abstract

Alcohol use disorder (AUD) has been frequently associated with high stress sensitivity and impulse control problems (Sinha 2008; Potenza & de Wit, 2010). However, neural mechanisms underlying stress, impulsivity, and alcoholism remain unclear. Using functional magnetic resonance imaging, the current study investigated stress-related neural correlates and connectivity underlying impulse control difficulties in demographically-matched, 37 (8 women) AUD patients and 37 (13 women) healthy controls during brief imagery trials of stress, alcohol, and neutral-relaxing cues (mean age=35.7 (s.d.=8.3). AUD patients had higher scores on a subscale of impulse control difficulties compared to controls (p=.016), measured by Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004). Whole-brain correlation results indicated that impulse control problems were significantly associated with hypoactive response to stress in key brain regions of emotion regulation, including the ventromedial prefrontal cortex, caudate, and left dorsolateral prefrontal cortex (DLPFC) ($p<0.01$, whole brain corrected). Subsequently, functional connectivity was examined with these correlates as seed regions. Among these, the left DLPFC seed resulted in significant group difference by showing decreased connectivity with the dorsomedial PFC (DmPFC), but increased connectivity with sensory and motor cortices in AUD patients, even after controlling for co-occurring smoking behaviors ($p<0.05$, whole-brain corrected). Reduced connectivity between the left DLPFC and DmPFC was further associated with increased stress anxiety ratings in AUD patients ($p<0.05$, corrected). The left DLPFC is involved in executive and cognitive control, whereas the DmPFC is involved in evaluation and modulation of emotion, suggesting that a reduced interaction between regions of executive control