these substrates in the PPI-disruptive effects of NMDA. Replication studies are in progress, as are studies designed to distinguish the contribution of the VS and EC to the PPI-disruptive effects of NMDA infusion within the HPC.

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121. TOWARDS THE GENETICS OF A COMPLEX PHENOTYPE: STRAIN ANALYSES OF DRUG EFFECTS ON STARTLE GATING


Department of Psychiatry, UCSD School of Medicine, 9500 Gilman Dr., La Jolla, CA 92093-0804

Sensorimotor gating of the startle reflex, measured by PPI, is impaired in humans with specific neuropsychiatric disorders, and is disrupted in humans and rats by dopamine (DA) agonists. Animal models are clarifying the genetics of PPI and its sensitivity to neurochemical regulation. Differences in sensitivity to the PPI-disruptive effects of APO across rat strains (eg. Sprague Dawley (SD) vs. Wistar (W)), and within strains, across suppliers (eg. Harlan ["H"] vs. Bantin-Kingman ["BK"]) must reflect relatively subtle genetic drift, which might be manipulated by pharmacogenetic strategies and serve as targets for QTL or other approaches for understanding the genetics of complex phenotypes.

We assessed the scope and development of PPI APO sensitivity differences in SD vs. W rats (H and BK). Findings confirmed significant SDH > WH sensitivity to the PPI-disruptive effects of APO in adults and d18 pups; an SDH × WH F1 exhibited the WH parental phenotype. Both BK rat strains were less sensitive than SDH rats to the PPI-disruptive effects of APO; in SDBKs, APO effects on PPI interacted with changes in startle magnitude. SDH > SDBK sensitivity was also noted in the PPI-disruptive effects of the D1 agonist SKF82958, but not the D2 agonist quinpirole. Substrain differences in PPI drug sensitivity are DA receptor subtype-specific. SDH > WH APO sensitivity in d18 pups suggests that genetic differences in DAergic sensitivity are expressed early in development; for this substrate, efficient phenotype screening can be completed in pups.

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122. EFFECTS OF CAFFEINE ON SENSORIMOTOR GATING OF THE STARTLE REFLEX IN NORMAL CONTROL SUBJECTS


Department of Psychiatry, UCSD School of Medicine, 9500 Gilman Dr., La Jolla, CA 92093-0804

Prepulse inhibition (PPI), a cross-species measure of sensorimotor gating, is impaired in certain neuropsychiatric disorders. This study was designed to assess caffeine effects on PPI in normal humans, as part of an effort to understand cross-species differences and similarities in the neurochemical regulation of PPI. Startle was measured during a screening session ("DAY 1"); 7–10d later, subjects were restested ("DAY 2") after placebo or caffeine (200 mg; double-blind design). Subjects, characterized as low vs. high caffeine drinkers (LOCAF vs. HICAF) based on established scales, refrained from ad libitum caffeine consumption for ≥ 15h prior to DAY 2 testing. Autonomic and self-rating measures, acoustic and tactile startle, and unimodal and cross-modal PPI, were measured in divided sessions for 3h post-treatment. On DAY 2, there were significant effects of caffeine on autonomic measures but not acoustic or tactile startle magnitude, habituation or PPI. HICAF subjects reported withdrawal symptoms after placebo that were blunted by caffeine. Compared to DAY 1 measures, DAY 2 PPI was greater in LOCAF subjects after placebo, and in HICAF subjects after caffeine. The opposite pattern was also true: LOCAF subjects exhibited less PPI after caffeine, and HICAF subjects exhibited less PPI after placebo, on DAY 2 vs. DAY 1. Thus, caffeine withdrawal, evident in HICAF subjects after placebo, may be accompanied by reduced PPI. A new study is in progress in which subjects maintain ad libitum caffeine intake to blunt any impact of caffeine withdrawal on startle.

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123. CEREBELLAR GRAY MATTER VOLUME DEFICITS IN SCHIZOPHRENIA AND ALCOHOLISM


(1) Department of Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA; (2) Psychiatry Service, VA Health Care System; (3) Departments of Psychology and Radiology, Stanford University; (4) Neuropsychiatry Program, SRI International; (5) Nathan Kline Institute for Psychiatric Research

Cerebellar pathology may contribute to the pathophysiology of schizophrenia, yet it remains controversial whether cerebellar dysmophlogy occurs in schizophrenia and, if it does, what specifically is affected. Complicating this search is the high incidence of alcohol abuse in schizophrenia that can contribute to cerebellar pathology, most notably in anterior superior vermis.

To examine these issues, we used thin-slice, 3D MRI to study 61 normal control men (NC), 25 alcoholic men (ALC), 27 schizophrenia men (SZ), and 19 men comorbid for schizophrenia and alcohol abuse (SZ + ALC). Cerebellar structures were manually outlined, tissue classification was statistically determined, and regional volumes were corrected for normal variation in head size and age.

SZ had enlarged fourth ventricles but not cerebellar tissue volume deficits. ALC had gray and white matter vermicul deficits (most prominent in the anterior superior lobules) and gray matter hemisphere deficits, but not fourth ventricle enlargement. SZ + ALC had cerebellar hemisphere and vermic gray matter volume deficits and fourth ventricular enlargement to a greater extent than did either single diagnosis group, despite relatively low levels of alcohol consumption of the SZ + ALC compared to the ALC group. Gray matter volume in the anterior superior vermis correlated with lifetime alcohol consumption in the total group of schizophrenic patients.

These data support the contention that even relatively modest levels of alcohol consumption is a major factor underlying cerebellar volume deficits in schizophrenia. Consequently, schizophrenics may have cerebellar supersensitivity to the detrimental effects of alcohol, with added risk of motor and cognitive dysfunction common to both diseases.

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