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Characterization of the effects of corticotropin-releasing factor on prepulse inhibition of the acoustic startle response in Brown Norway and Wistar-Kyoto rats

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Abstract

Sensori-motor gating, as assessed by prepulse inhibition of the startle response is diminished in patients with schizophrenia. We have previously shown that inbred Brown Norway (BN) rats display significantly less prepulse inhibition of the acoustic startle response than inbred Wistar-Kyoto (WKY) rats, and that prepulse inhibition is decreased by central administration of the neuropeptide, corticotropin-releasing factor (CRF) in both strains. The present study was conducted to establish whether peripheral administration of CRF alters prepulse inhibition, whether a low, threshold dose for decreasing prepulse inhibition is the same in the two rat strains, and whether central administration of a CRF receptor antagonist enhances prepulse inhibition in the BN strain. CRF-induced behavioral activation was also examined to determine whether the two rat strains are differentially sensitive to a behavioral effect of CRF that does not involve the startle response. In each experiment, BN rats showed significantly less prepulse inhibition than WKY rats. Subcutaneous administration of CRF had no affect on startle amplitude or prepulse inhibition of the startle response in either rat strain. In BN, but not in WKY rats, low-dose CRF (0.3 μg) decreased prepulse inhibition. However, doses of CRF that did not alter prepulse inhibition in the WKY strain, did result in behavioral activation. No dose of CRF tested affected baseline startle amplitude. Central administration of the CRF receptor antagonist, astressin had no effect on prepulse inhibition or startle amplitude in either rat strain. Central administration of the CRF receptor antagonist, D-Phe CRF $_{12–41}$ had no effect on prepulse inhibition in WKY rats, resulted in a only a small, non-significant increase in prepulse inhibition in BN rats, while it decreased startle amplitude. The results suggest that CRF reduces prepulse inhibition of the acoustic startle response independently of effects on the pituitary-adrenal axis, and that endogenous CRF has at most, a minor role in the low prepulse inhibition found in BN rats.

Keywords: Brown Norway rat; Schizophrenia; Sensorimotor gating; Startle amplitude; Wistar-Kyoto rat

1. Introduction

Presentation of a non-startling stimulus, shortly prior to presentation of a startling stimulus, results in inhibition of the startle response (Hoffman and Searle, 1965), a phenomenon known as prepulse inhibition. Prepulse inhibition is measure of sensori-motor gating that is thought to occur so that processing of the prepulse stimulus is not disrupted by a large-amplitude startle response, and deficits in prepulse inhibition might reflect a deficit in the ability to integrate information (Braff and Geyer, 1990). Prepulse inhibition is diminished in patients with a number of psychiatric disorders including schizophrenia (Braff et al., 1978; Geyer et al., 1990; Mackeprang et al., 2002; Parwani et al., 2000), as well as in the unaffected relatives of patients with schizophrenia (Cadenhead et al., 2000), suggesting a genetic influence. Indeed in persons with no psychiatric diagnosis, prepulse inhibition is highly heritable (Anokhin et al., 2003).

In rodents, prepulse inhibition of the acoustic startle response can be achieved using parameters that are nearly identical to those employed in studies with human subjects,

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making the paradigm a useful tool for studying the roles of specific neurotransmitters and genetic influences in sensorimotor gating deficits. Drugs that increase extracellular concentrations of dopamine, or are dopamine receptor agonists, disrupt prepulse inhibition in rats (Geyer et al., 1990; Mansbach et al., 1988). Serotonin (5-HT) releasers, and direct agonists at 5-HT_{1B} or 5-HT_2 receptors, also decrease prepulse inhibition in rodents (Martinez and Geyer, 1997; also see Swerdlow and Geyer, 1998 for review). In the absence of pharmacological manipulations, there are differences in prepulse inhibition among rat strains (Faraday et al., 1999; Hall et al., 1997; Varty and Geyer, 1998). Additionally, there are rat strain differences in sensitivity to the disruptive effects of dopamine receptor agonists on prepulse inhibition (Swerdlow et al., 2000; Varty and Geyer, 1998).

We have shown that inbred Brown Norway (BN) rats show significantly less prepulse inhibition than inbred Wistar-Kyoto (WKY) rats (Palmer et al., 2000; Conti et al., 2002), and that central administration of a relatively high dose of corticotropin-releasing factor (CRF) diminishes prepulse inhibition in both the BN and WKY strains. While CRF is a hypothalamic peptide that is released during stress to result in adrenocorticotropic hormone (ACTH) release, (Rivier and Vale, 1983), CRF from non-hypothalamic sources acts as a neurotransmitter during stress (Gabr et al., 1991; Van Bockstaele et al., 1998). CRF-immunoreactive cells and fibers are distributed in many regions of the brain, including the central nucleus of the amygdala, the hippocampus, the cortex, and the dorsal raphe nucleus (Kirby et al., 2000; Lahmame et al., 1997; Swanson et al., 1983). CRF receptors are expressed in cortex, striatum, hippocampus, the nucleus accumbens, and the basolateral nucleus of the amygdala (Chalmers et al., 1995; De Souza, 1987; Radulovic et al., 1998), areas shown to be important for regulation of prepulse inhibition (Bakshi and Geyer, 1999; Swerdlow et al., 1994).

The reason for the low basal prepulse inhibition in the BN rat strain is not known. One possibility is that BN rats show low levels of prepulse inhibition because they have higher levels of endogenous CRF in cortex than WKY rats (Lahmame et al., 1997). Indeed, transgenic mice which overexpress CRF show diminished prepulse inhibition compared to wild-type controls (Dirks et al., 2002). If high endogenous levels of CRF result in the relatively poor prepulse inhibition in the BN strain, then central administration of a CRF receptor antagonist might improve prepulse inhibition in this strain.

The present studies were designed to further investigate the role of CRF on prepulse inhibition in the WKY and BN rat strains by asking three questions: (1) Dose peripheral administration of CRF, at doses that result in activation of the hypothalamic–pituitary–adrenal axis (Cador et al., 1992), also decrease prepulse inhibition?; (2) Is there a differential effect of CRF on prepulse inhibition in WKY and BN rats at doses of CRF that are considerably lower than those previously used?; (3) Does central administration of a CRF receptor antagonist enhance the low levels of prepulse inhibition seen in the BN rat strain?

2. Materials and methods

2.1. Animals

Experiment 1 was performed while the author was at the University of California, San Diego (UCSD), and experiments 2 and 3 were performed at the University of Connecticut Health Center (UCHC). Rats for all experiments were males, weighing 250–275 g at the start of the experiment. WKY rats were obtained from Charles River, and Brown Norway rats were obtained from Harlan, Sprague Dawley. Rats were allowed to acclimate to our vivarium for 1 week prior to the start of any experimental procedure. The vivaria at both UCSD and UCHC are maintained on a 12 h light/dark cycle with laboratory chow and water available ad libitum. All rats were housed 2–3/cage until undergoing surgery to have intracerebroventricular (i.c.v.) cannula implanted (experiments 2 and 3). Thereafter, the rats were single-housed for 5–7 days until testing. All procedures were in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Surgery to implant i.c.v. guide cannula

In experiments 2 and 3, rats were anesthetized with a mixture of isoflurane-in-air (1.5%) and placed into a stereotaxic instrument equipped with blunt ear bars. A stainless-steel guide cannula (22 gauge) was aimed at the lateral ventricle (1.0 mm posterior and 2.0 mm lateral to Bregma) for subsequent i.c.v. infusion of either saline, hCRF (experiment 2), or one of two CRF receptor antagonists (experiment 3). Two jewelers' screws were placed into the skull, and the entire assembly was held in place with dental cement. Testing occurred following a 5–7 day recovery period.

2.3. CRF and CRF receptor antagonists

Both hCRF, and the CRF receptor antagonists, cyclo(30–33)D-Phe^{12},$Nle^{21,38}$,Glu^{30},Lys^{33}r$CRF_{-(12-41)}$ (astressin), and D-Phe^{12}, $Nle^{21,38}$,$C^{\alpha}Me$ Leu^{37}r$CRF_{(12-41)}$ (D-Phe) were kindly provided by Dr. Jean Rivier (Salk Institute, La Jolla, CA).

2.4. CRF and CRF receptor antagonist administration and observation of active behaviors

In experiment 1, rats received a subcutaneous (s.c.) injection of either saline or CRF (1.0 or 3.0 μg; 1.0 ml/kg volume) 30 min prior to testing. For i.c.v. infusions in experiments 2 and 3, rats were gently held while an infusion