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Research Report

Disruption of thermal nociceptive behaviour in mice mutant for the schizophrenia-associated genes NRG1, COMT and DISC1

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ABSTRACT

Abnormalities in pain perception, especially altered warmth and heat pain sensitivity, have been reported in schizophrenia. Therefore, genes associated with schizophrenia, including neuregulin-1 (NRG1), catechol-O-methyltranferase (COMT) and disrupted-in-schizophrenia-1 (DISC1), may play a role in modulating the physiological and psychological effects of pain stimuli in such patients. Thermal pain sensitivity was assessed in NRG1, COMT and DISC1 mutant mice, and the anti-nociceptive effects of acute Δ^9-tetrahydrocannabinol (THC) were compared in NRG1 and COMT mutants. At baseline, deletion of NRG1 and DISC1 each reduced thermal pain sensitivity, while deletion of COMT increased pain sensitivity. Neither NRG1 nor COMT deletion altered the anti-nociceptive effects of acute systemic THC (8.0 mg/kg). These results indicate a differential contribution of NRG1 and DISC1 vis-à-vis COMT to the processing of thermal nociceptive stimuli and extend their phenotypic relationship to psychotic illness.

1. Introduction

A number of candidate genes have now been reported to confer increased risk for schizophrenia, as documented in recent systematic reviews and meta-analyses (Allen et al., 2008; Shi et al., 2008). Among these, variation in the neuregulin-1 (NRG1) gene has been implicated in risk for schizophrenia, although the functional variant has yet to be identified (Mei and Xiong, 2008; Munafo et al., 2008; Gong et al., 2009). Familial mutation in the disrupted-in-schizophrenia-1 (DISC1) gene, due to a balanced chromosomal translocation at 1q42.1-1q42.3, has been associated with schizophrenia and other psychiatric disorders across diverse populations (Chubb et al., 2008; Muir et al., 2008). While evidence associating the catechol-O-methyltranferase (COMT) gene with risk for schizophrenia is less clear (Allen et al., 2008; Okochi et al.,

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Abbreviations: ANOVA, analysis of variance; COMT, catechol-O-methyltranferase; DISC1, disrupted-in-schizophrenia-1; ENU, N-ethyl-N-nitrosourea; NRG1, neuregulin-1; S.E.M., standard error of the mean; THC, Δ^9-tetrahydrocannabinol

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2009), it has also been implicated in a cognitive endophenotype (Tunbridge et al., 2006; Barnett et al., 2008).

Both historical and contemporary reviews of abnormal pain perception in schizophrenia indicate decreased pain sensitivity in more than 50% of patients, with the majority of studies suggesting some abnormality in pain or thermal perception (Dworkin, 1994; Singh et al., 2006). Differences in pain sensitivity have also been documented in both pharmacologically and environmentally based animal models of schizophrenia (Becker et al., 2006; Tuboly et al., 2009). The NRG1 and COMT genes may play a role in pain modulation. NRG1 has been shown to be a pro-nociceptive cytokine; intrathecal administration of recombinant NRG1-beta1 protein significantly decreased the hindpaw tactile withdrawal threshold in rats (Lacroix-Fralish et al., 2008). Additionally, a recent study demonstrated an increase in NRG1 expression in the dorsal horn following experimentally induced peripheral nerve injury (Calvo et al., 2010) . Disruption of the NRG1–erbB signalling pathway may contribute to the pathogenesis of peripheral neuropathies, with hypomyelination and neuropathic pain (Chen et al., 2006). Pharmacological inhibition of COMT in rats is associated with increased pain sensitivity (Nackley et al., 2007). In mutant mice bearing targeted mutation of COMT, increased COMT activity attenuated pain perception, while reduced COMT activity increased pain perception (Papaleo et al., 2008). However, another study in COMT knockout mice reported no difference in pain sensitivity (Kambur et al., 2008). Pain sensitivity has yet to be assessed systematically in mice containing mutation of the DISC1 gene.

Δ^9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, is known to exert anti-nociceptive effects in both rodents and humans (Kunos et al., 2009; Karst and Wippermann, 2009). Psychomotor effects of THC in rodents are influenced by NRG1 deletion (Boucher et al., 2007) and the association between THC exposure and risk for psychosis in humans is influenced by COMT genotype (Caspi et al., 2005). However, whether NRG1 and COMT might influence other psychopharmacological actions of THC remains unknown (Desbonnet et al., 2009; Kirby et al., 2009). Thus, the aims of this study were (a) to systematically assess and compare thermal pain sensitivity in mice with heterozygous deletion of NRG1, heterozygous deletion or homozygous knockout of COMT, and heterozygous or homozygous mutation of mouse DISC1, and (b) to examine the anti-nociceptive effects of acute THC in NRG1 and COMT mutants.

2. Results

2.1. *Nociception at baseline*

Hot plate and tail flick assays at baseline involved 41 NRG1 WT (16 male, 25 female) and 37 NRG1 HET (10 male, 27 female); 27 COMT WT (18 male, 9 female), 27 COMT HET (13 male, 14 female) and 39 COMT KO (11 male, 28 female); 20 DISC1 WT (10 male, 10 female), 20 DISC1 HET (10 male, 10 female), 20 DISC1 KO (10 male, 10 female). All animals were between 3 and 10 months of age at testing and neither mean age nor body weight differed between the genotypes. In baseline studies, tail flick data were not collected for 3 and 4 mice in the NRG1 and COMT groups, respectively, due to poor habituation to the restraint apparatus.

In NRG1 mutants, hot plate latency was increased [effect of genotype: $F(1,74)=3.82$, $p=0.05$; no effect of sex or genotype × sex interaction (Fig. 1A)]. Tail flick latency was also increased in NRG1 HET [effect of genotype: $F(1,71)=5.78$, $p<0.05$ (Fig. 1B)], with males demonstrating an increase in tail flick latencies relative to females which just failed to reach statistical significance [effect of sex, $F(1,71)=26.18$, $p<0.001$; genotype × sex interaction, $F(1,71)=3.34$, $p=0.07$].

In COMT mutants, while hot plate latency was unaltered [no effect of genotype or sex; no genotype × sex interaction (Fig. 2A)], tail flick latency differed between the genotypes [effect of genotype, $F(2,86)=3.90$, $p<0.05$; no effect of sex or genotype × sex interaction (Fig. 2B)]; tail flick latencies in COMT KO were lower than in HET [$t(62)=2.57$, $p<0.05$] and WT [$t(61)=1.91$, $p=0.06$], although the latter comparison proved only marginally significant.

In DISC1 mutants, hot plate latency differed between the genotypes [effect of genotype: $F(2,56)=9.96$, $p<0.001$; no effect of sex or genotype × sex interaction (Fig. 3A)]; hot plate latencies in DISC1 HET [$t(40)=3.70$, $p<0.01$] and homozygous mutants [$t(39)=3.94$, $p<0.01$] were higher than in WT. Tail flick latency also differed between the genotypes [effect of genotype: $F(2,56)=3.87$, $p<0.05$ (Fig. 3B)], with males having higher tail flick latencies than females [effect of sex: $F(1,56)=2.30$, $p<0.05$; no genotype × sex interaction]; tail flick latencies in DISC1 homozygous mutants were higher than in HET [$t(39)=2.22$, $p<0.05$] and WT [$t(41)=2.40$, $p<0.05$].

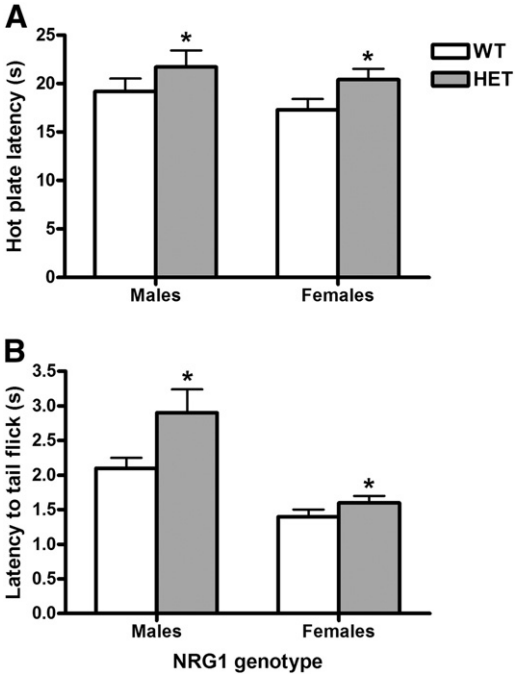

Fig. 1 – Baseline latencies (s) in (A) hot plate and (B) tail flick tests for male and female wildtype (WT; $n=16$ males, 23 females) and NRG1 heterozygous (HET; $n=10$ males, 27 females) mutants. Data are means ± SEM; $^*p<0.05$, HET vs. WT.