Interleukin-6 induces spatially dependent whole-body hypersensitivity in rats: implications for extracephalic hypersensitivity in migraine

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Research article

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Abstract

Background: Migraine is a complex neurological disorder that is characterized by throbbing head pain, increased sensitivity to light, sound, and touch, as well as nausea and fatigue. It is one of the most common and most disabling disorders globally but mechanisms causing migraine are poorly understood. While head pain is a typical feature of attacks, they also often present with cutaneous hypersensitivity in the rest of the body. In contrast, pain conditions in the lower parts of the body do not generally lead to cutaneous hypersensitivity in the head. Previous studies indicate that application of stimuli to the meninges of rodents causes cutaneous facial as well as hindpaw hypersensitivity. In the present study, we asked whether widespread hypersensitivity is a unique feature of dural stimulation or whether body-wide responses occur similarly when the same stimulus is given in other locations.

Methods: Rats were given the same dose of IL-6 either via dural, intraplantar, subcutaneous, intramuscular, intracisternal, or intrathecal injection. Cutaneous facial and hindpaw allodynia was assessed using Von Frey following injection into each location.

Results: Hindpaw allodynia was observed following dural and intraplantar injection of IL-6 in both males and females. Hindpaw allodynia was only observed in females following intracisternal and intrathecal IL-6 injections. In contrast, facial allodynia was only observed in either sex following dural and intracisternal injections, which would activate meningeal afferents and the trigeminal nucleus caudalis (TNC), respectively.

Conclusions : Here we show that while stimulation of upper body regions with IL-6 including the meninges and brainstem can cause widespread hypersensitivity spreading to the paws, similar stimulation of the lower body does not cause the spread of hypersensitivity into the head. These data are consistent with the observations that whole body hypersensitivity is specific to conditions such as migraine where pain is present in the head and they may provide insight into co-morbid pain states associated with migraine.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures

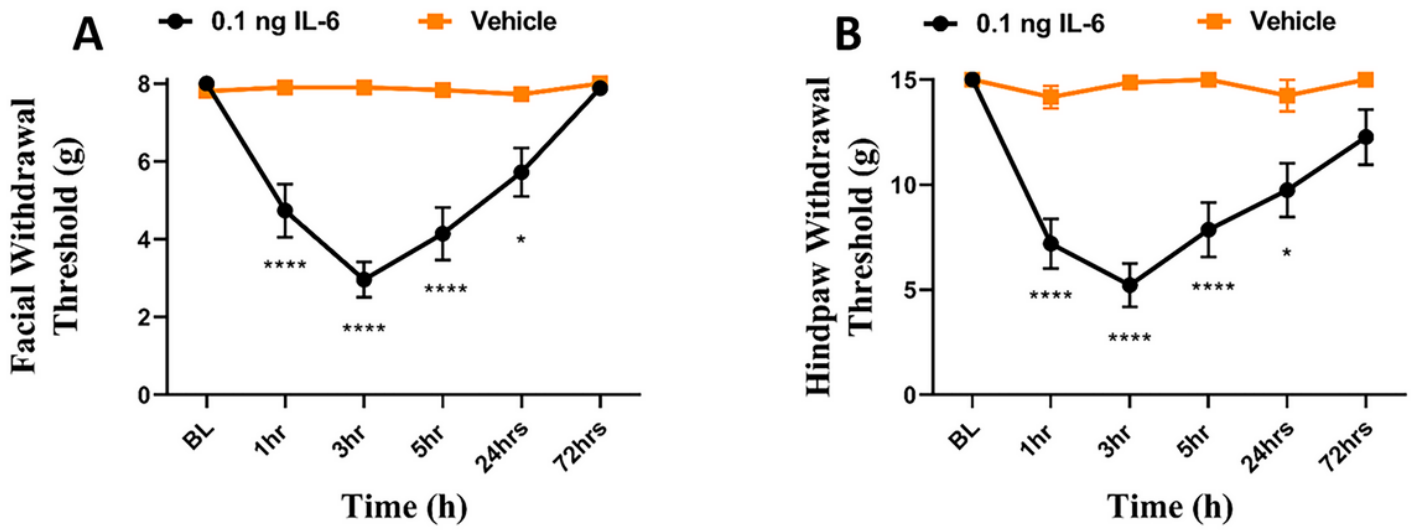

Figure 1

Dural IL-6 produces facial and hindpaw hypersensitivity in females. Female rats had baseline withdrawal thresholds established prior to receiving administration of 0.1 ng IL-6 onto the dura. Dural IL-6 (n=10) elicited significant effect of treatment on facial (A) $F(1, 66) = 31.58$, $p<0.0001$) and hindpaw (B) ($F(1, 66) = 43.66$, $p<0.0001$) hypersensitivity when compared with animals that received vehicle (n=4). *$p<0.05$, ****$p<0.0001$.

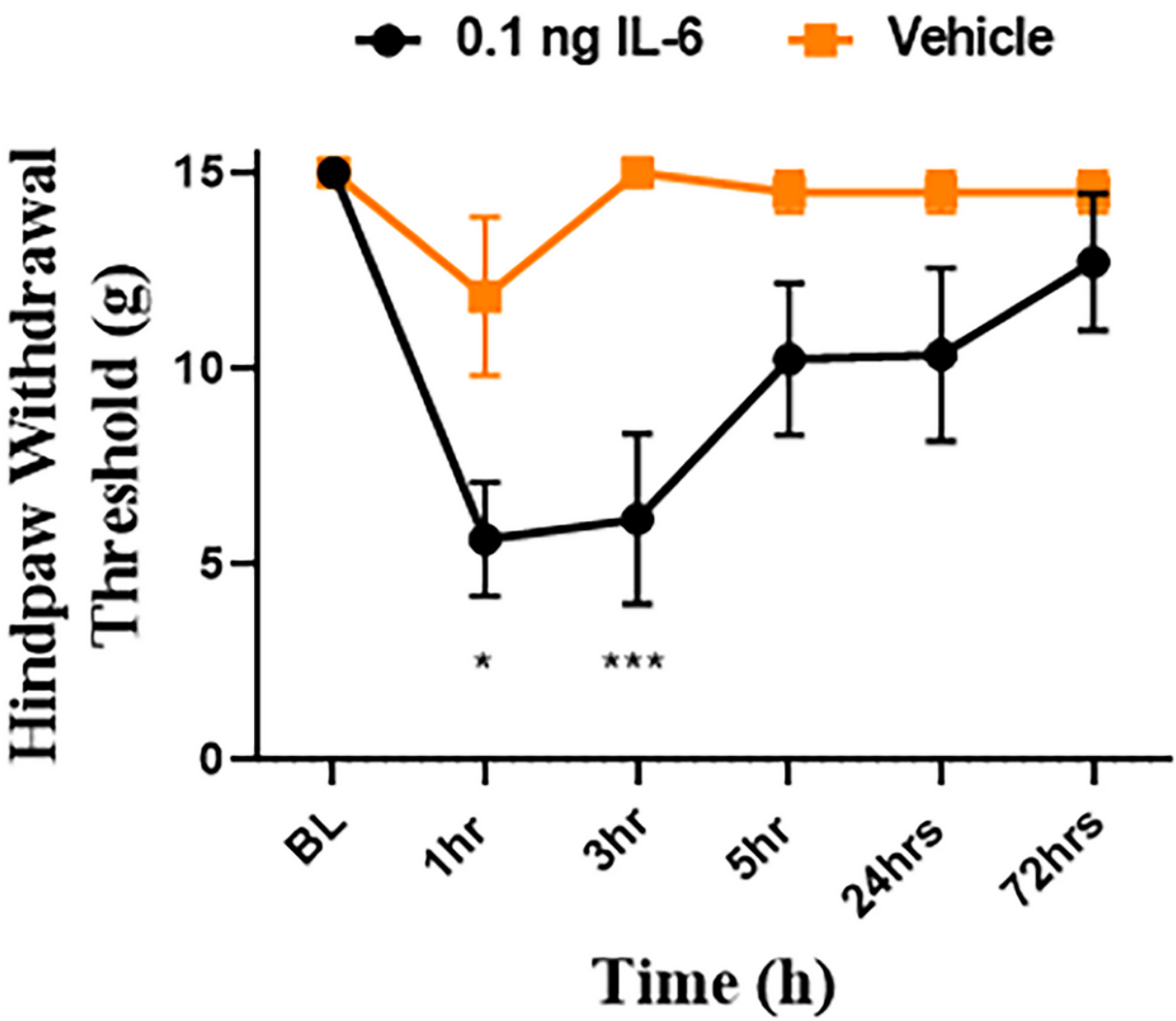

Figure 2

Intraplantar IL-6 produces hindpaw hypersensitivity in females. Female rats from the cohort in figure 2 also had baseline hindpaw withdrawal thresholds established prior to receiving intraplantar injection of 0.1 ng IL-6. IL-6 (n=6) elicited significant effect of treatment on hindpaw hypersensitivity ($F(5, 60) = 2.512$, $p=0.0394$) when compared with animals that received vehicle (n=6). *$p<0.05$, ***$p<0.001$.

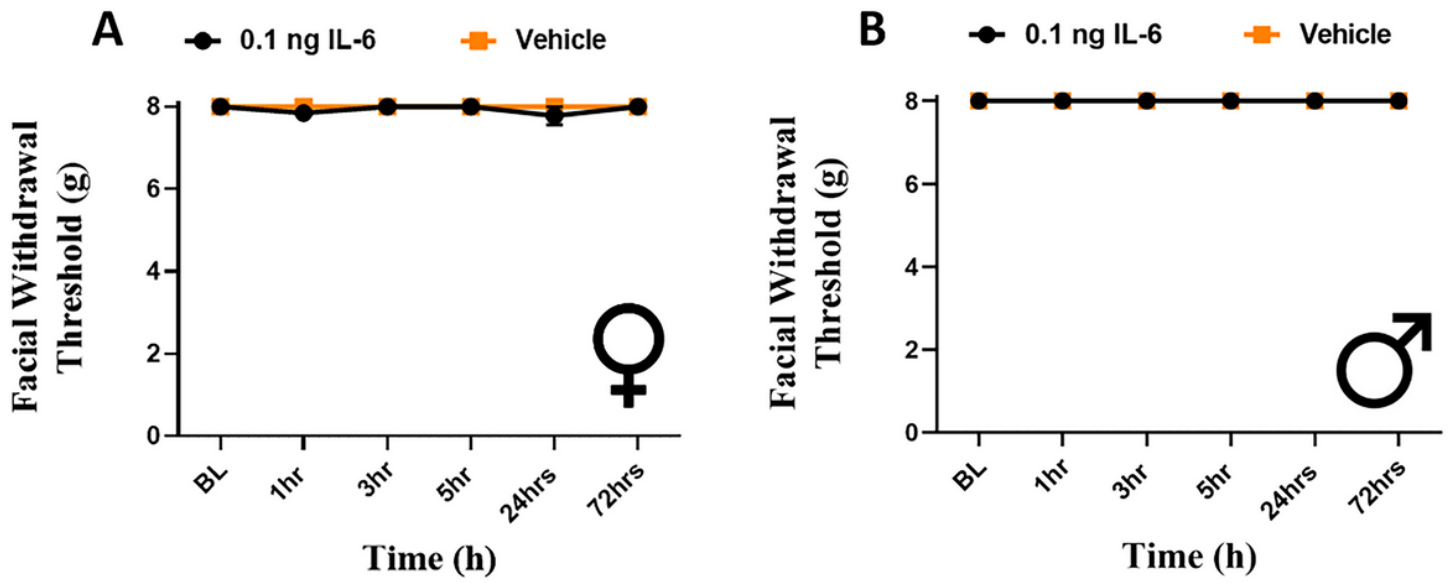

Figure 3

Intraplantar administration of IL-6 produces no facial responses in female or male rats. Female and male rats had facial hindpaw withdrawal thresholds assessed prior to and following intraplantar injection of 0.1 ng IL-6 (6 females, 6 males) or vehicle (6 females, 6 males). Two-way ANOVA followed by Bonferroni posthoc analysis revealed no significant facial responses in female (A) ($F(1, 40) = 1.844$, $p=0.1821$) or male (B) (no variation among groups) rats.

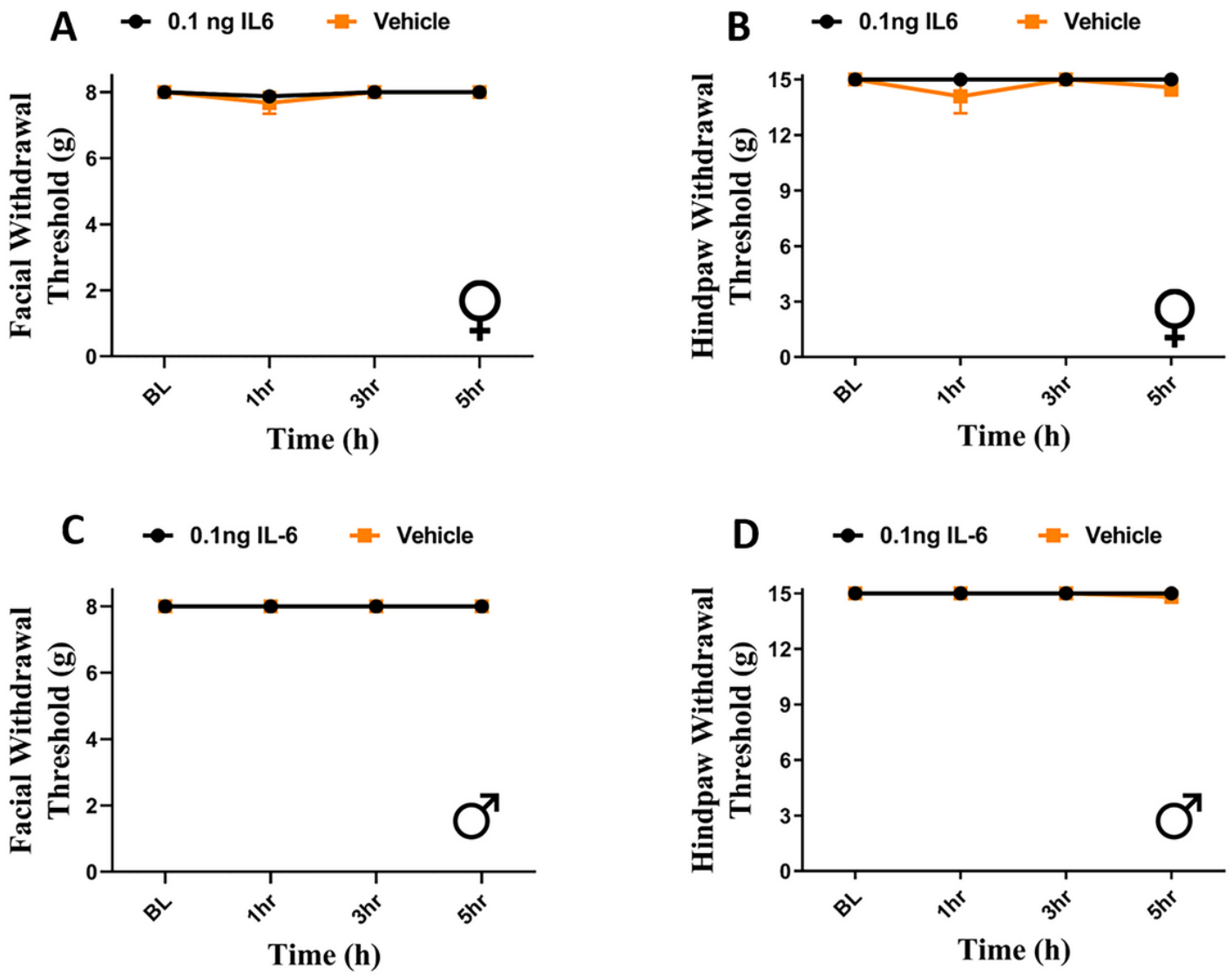

Figure 4

Subcutaneous injection of IL-6 in the scalp produces no significant facial or hindpaw responses in male and female rats. Rats had facial and hindpaw withdrawal thresholds assessed to establish baseline withdrawal thresholds, as well as following administration of 0.1 ng IL-6 (6 females, 8 males) or vehicle (7 females, 6 males) subcutaneously in the scalp. Two-way ANOVA followed by Bonferroni posthoc analysis revealed no significant facial or hindpaw responses in female (A, B) ($F(1, 44) = 0.2761$, $p=0.6019$) ($F(1, 44) = 1.502$, $p=0.2269$) or male (C,D) (no variation among groups) ($F(1, 48) = 1.371$, $p=0.2473$) rats.

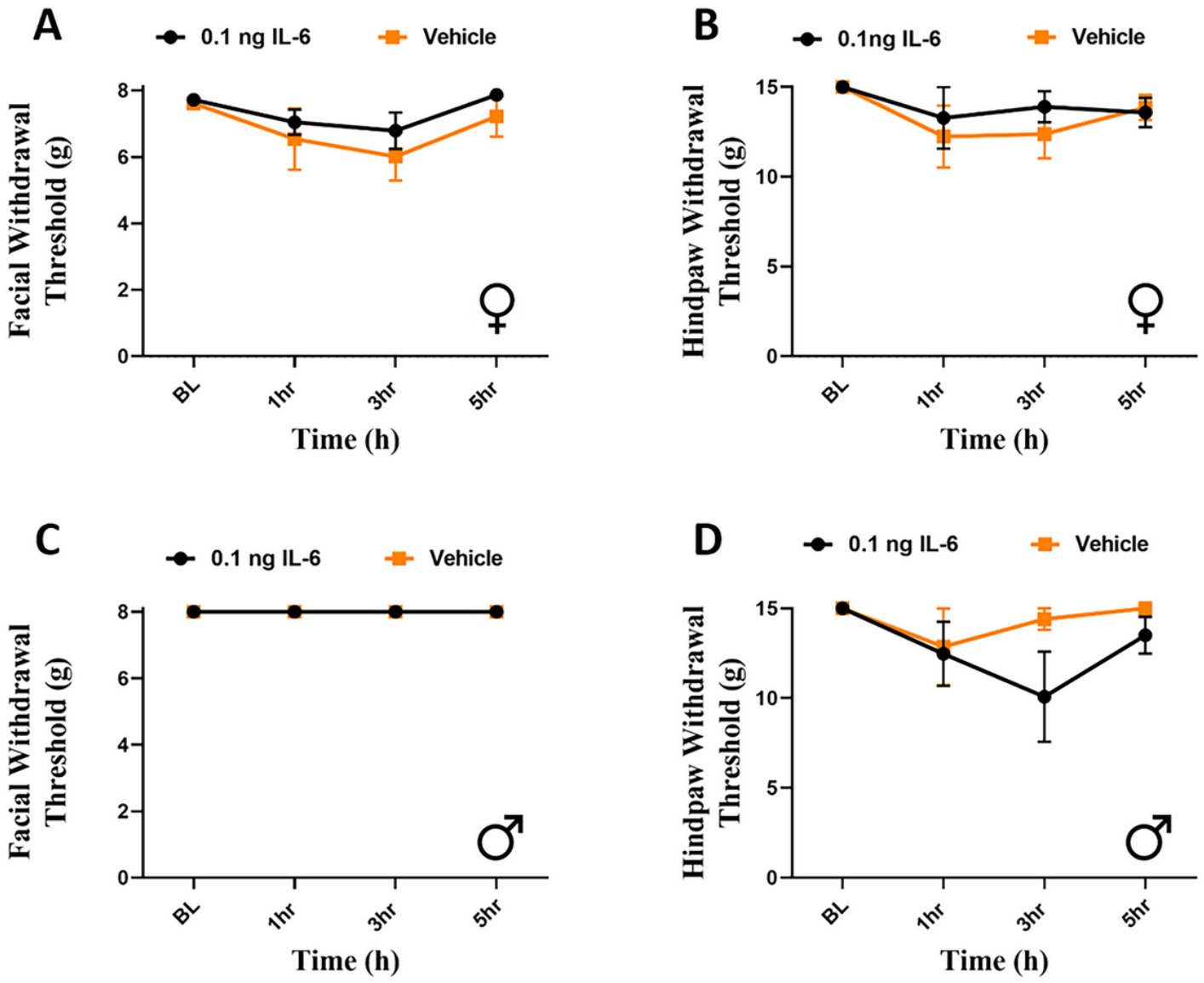

Figure 5

Gastrocnemius injection of IL-6 produces no significant facial or hindpaw responses in male and female rats. Rats had facial and hindpaw withdrawal thresholds assessed prior to and following administration of 0.1 ng IL-6 (6 females, 6 males) or vehicle (6 females, 5 males) into the gastrocnemius muscle. Two-way ANOVA followed by Bonferroni posthoc analysis revealed no significant effect of treatment on facial or hindpaw responses in female (A, B) ($F(1, 40) = 1.844$, $p=0.1821$) ($F(3, 36) = 0.2904$, $p=0.8320$) or male (C, D) (no variation among groups) ($F(1, 36) = 2.289$, $p=0.1390$) rats.

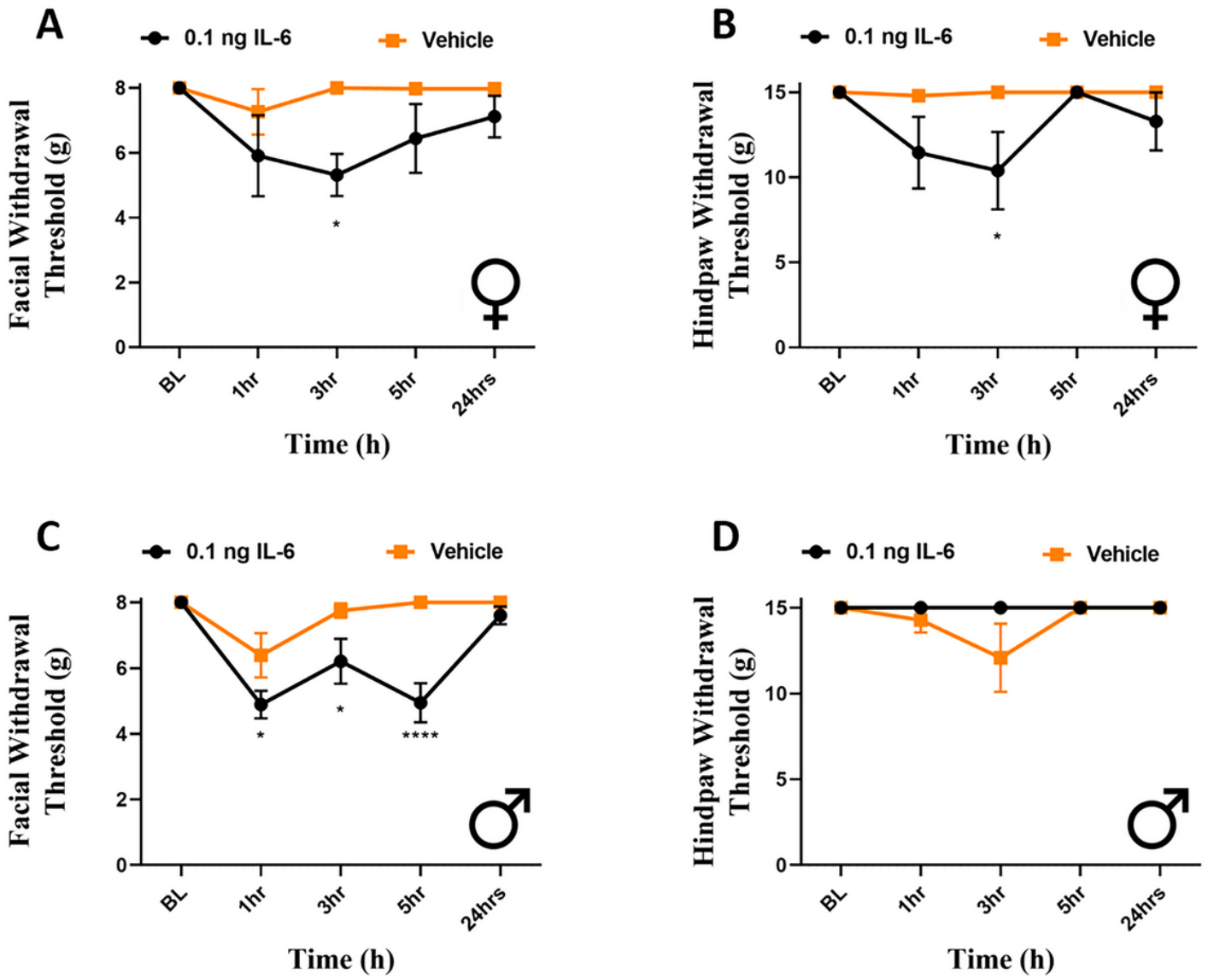

Figure 6

Intracisternal IL-6 produces facial hypersensitivity in both sexes, but differential hindpaw responses. Female (A, B) and male (C, D) rats had baseline withdrawal thresholds of the face and hindpaw determined prior to intracisternal injection of IL-6 (4 females, 6 males) or vehicle (5 females, 7 males). Both females and males demonstrated significant effects of treatment on facial responses ($F(1, 35) = 12.24$, $p=0.0013$) ($F(1, 55) = 27.98$, $p<.0001$); however, only females presented with hindpaw responses. ($F(1, 35) = 9.640$, $p=0.0038$) *$p<0.05$, ****$p<0.0001$.

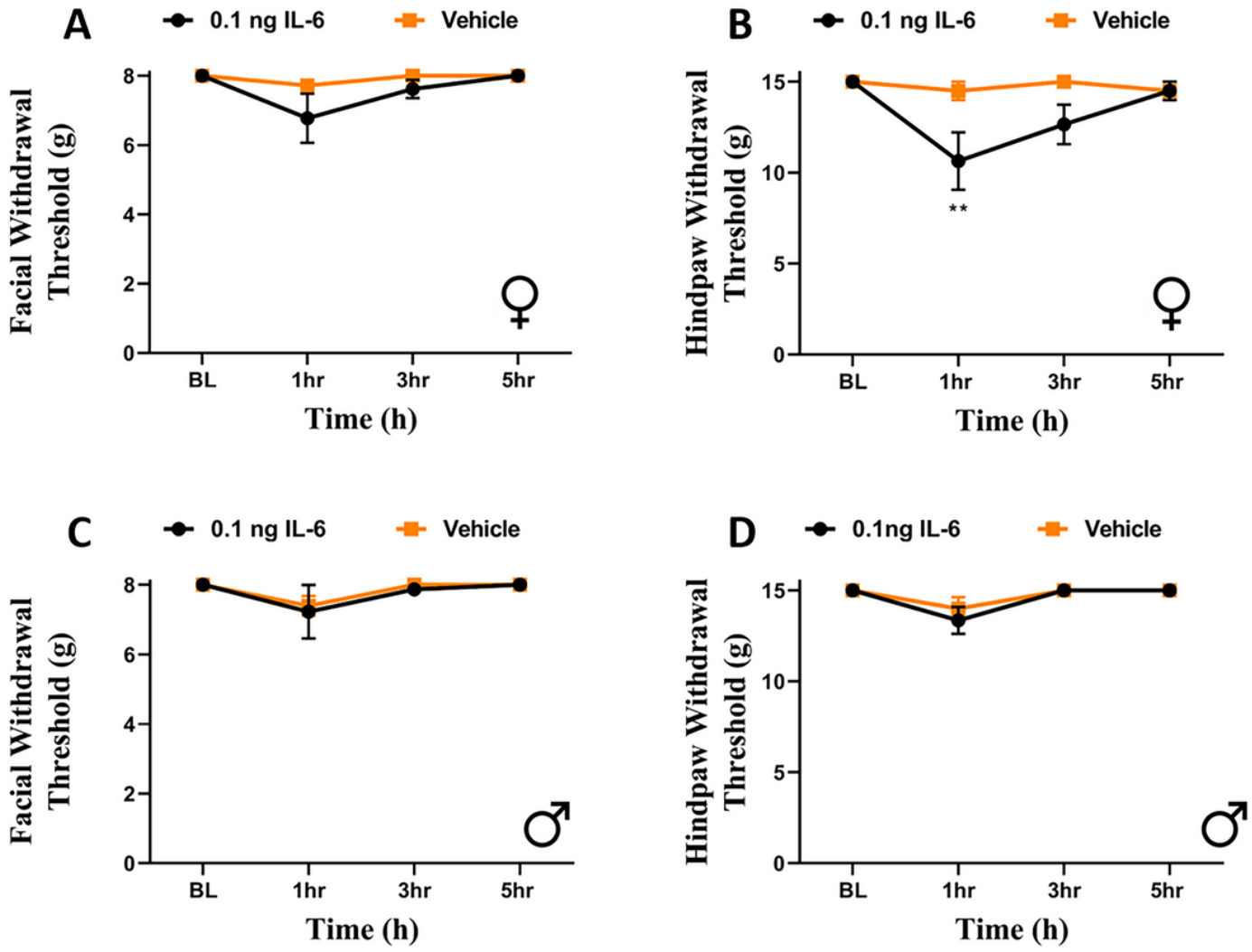

Figure 7

Intrathecal IL-6 produces hindpaw responses in female, but not male rats. Rats had periorbital and hindpaw withdrawal thresholds assessed prior to and following intrathecal administration of 0.1 ng IL-6 (6 females, 6 males) or vehicle (6 females, 6 males). Two-way ANOVA followed by Bonferroni posthoc analysis revealed no significant effect of treatment on facial responses in female (A, B) ($F(1, 40) = 2.924$, $p=0.0950$) or male (C, D) rats ($F(1, 40) = 1.280$, $p=0.7223$). Female rats demonstrated significant hindpaw allodynia. ($F(1, 40) = 8.700$, $p=0.0053$) $^{**}p<0.01$.