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Research Report

Cannabinoid CB2 receptor stimulation attenuates brain edema and neurological deficits in a germinal matrix hemorrhage rat model

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ABSTRACT

Germinal matrix hemorrhage (GMH) is one of the most common and devastating cerebrovascular events that affect premature infants, resulting in a significant socio-economic burden. However, GMH has been largely unpreventable, and clinical treatments are mostly inadequate. In the present study, we tested the hypothesis that JWH133, a selective CB2 receptor agonist, could attenuate brain injury and neurological deficits in a clostridial collagenase VII induced GMH model in seven-day-old (P7) S-D rat pups. Up to 1 h post-injury, the administration of JWH133 (1 mg/kg, intraperitoneal injection) significantly attenuated brain edema at 24 h post-GMH, which was reversed by a selective CB2R antagonist, SR144528 (3 mg/kg, intraperitoneal injection). Long-term brain morphology and neurofunctional outcomes were also improved. In contrast, JWH133 did not have a noticeable effect on the hematoma volume during the acute phase. These data also showed that microglia activation and inflammatory cytokine (TNF-α) release were significantly inhibited by JWH133 after GMH. This current study suggests a potential clinical utility for CB2R agonists as a potential therapy to reduce neurological injury and improve patient outcomes after GMH.

1. Introduction

Germinal matrix hemorrhage (GMH) is one of the most common neurological disorders in newborns, and it is defined as bleeding that arises from the subependymal (or periventricular) germinal region of the immature brain (Ballabh, 2010). It occurs in up to 20% of infants who are delivered at <32 weeks gestation. In the United States, >12,000 premature infants develop GMH every year (Hamilton et al., 2013), and studies have shown that infants who experience GMH can develop hydrocephalus or suffer from long-term neurologic dysfunction, including developmental delays, mental retardation, and cerebral palsy, all of which pose significant socioeconomic burdens (Ballabh, 2010). Because GMH has been largely unpreventable (Bassan, 2009; Roland and Hill,

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2003) and because clinical treatments are mostly inadequate (Kenet et al., 2011), it is clinically important to develop and test novel therapeutic strategies to mitigate these devastating neurological consequences.

The immunosuppressive and anti-inflammatory properties of marijuana-derived cannabinoids have been described in recent studies (Klein, 2005). Most of the effects of cannabinoids are mediated by the well-characterized heterotrimeric G-protein-coupled receptors cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R) (Nagarkatti et al., 2009; Whiteside et al., 2007). Whereas CB1R is highly expressed in the brain and causes the psychoactive effects of cannabinoids, CB2R activation was shown to protect against neuroinflammation (Bouaboula et al., 1996). Inflammatory activation is associated with neurological deficits in pre-clinical ICH models and with patient deterioration after clinical ICH (King et al., 2013). In fact, specific CB2R agonists attenuated brain edema both in traumatic brain injury animal models (Elliott et al., 2011) and following lipopolysaccharide-induced encephalitis (Ramirez et al., 2012). Furthermore, CB2R stimulation ameliorated neurological deficits and brain edema after experimental SAH in rats by reducing brain infiltration of leukocytes (Fujii et al., 2014). Although considerable evidence indicates the presence of functional CB2Rs in the CNS, the potential neuroprotective properties of these CB2Rs and the molecular mechanisms underlying the effects associated with their activation after GMH are not yet understood.

Therefore, the aim of the present study was to investigate the following experimental hypothesis: JWH133, a selective CB2R agonist, can inhibit microglia activation and inflammatory cytokine (TNF-α) release, which might reduce brain injury and attenuate neurological deficits after experimental GMH in neonatal rats.

2. Results

2.1. *JWH133 attenuated brain edema but did not reduce the hematoma volume at 24 h after GMH*

Brain water content, which is a measurement of brain edema, increased significantly in the right hemisphere of the vehicle group compared with the needle-only control pups (sham group) ($F=1.376$, $p<0.05$, $n=6$, Fig. 1B), and this phenotype was reversed by JWH133 ($F=1.600$, $p<0.05$, $n=6$, Fig. 1B). However, SR144528 administration increased the reduced brain water content ($F=1.802$, $p<0.05$, $n=6$, Fig. 1B). There were no distinct differences in the left hemispheres and cerebellums between the groups ($p>0.05$, $n=6$, Fig. 1B). Unfortunately, JWH133 did

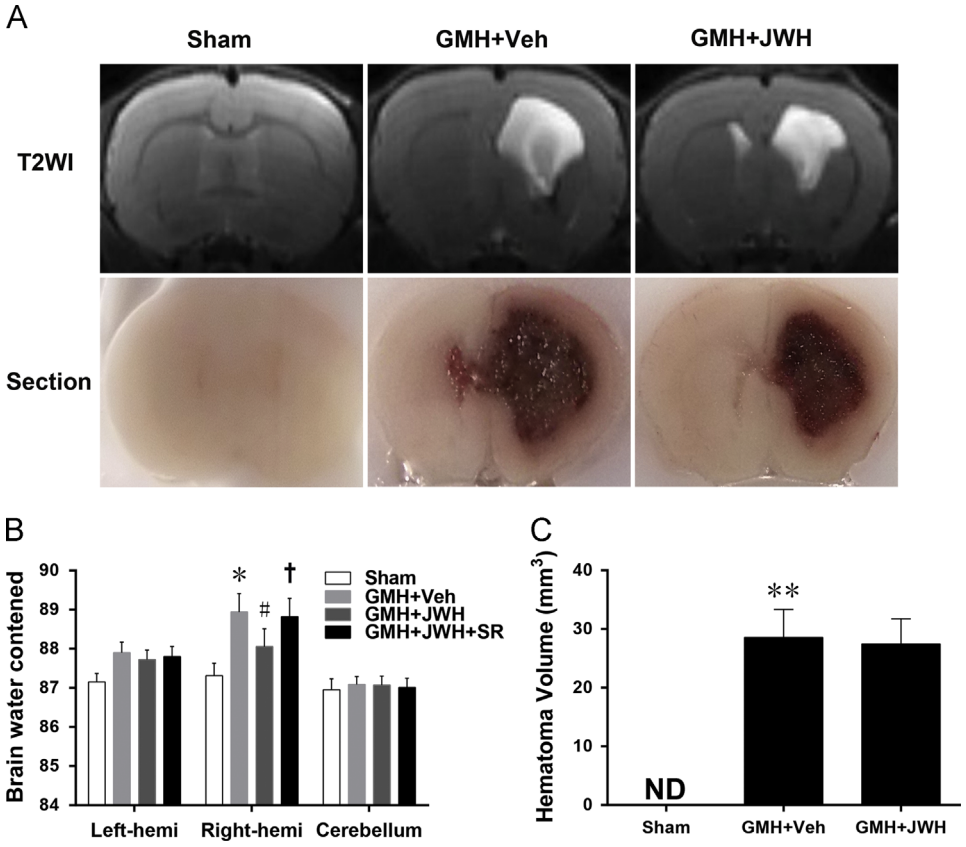

Fig. 1 – JWH133 attenuated brain edema, but it did not reduce the hematoma volume at 24 h post GMH. T2-weighted imaging and the sections of the cerebrals (A) showed the hematoma images. The brain water content (B) and hematoma volumes (C) at 24 h after surgery are displayed. The values are expressed as the means ± SD, $n=6$ per group. $^{*}p<0.05$, $^{**}p<0.01$ compared with sham, $p<0.05$ compared with vehicle, $^{\dagger}p<0.05$ compared with JWH133. F is a value in unpaired T test of the right hemisphere brain water content, df = 10.