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Dexmedetomidine ameliorates nocifensive behavior in humanized sickle cell mice

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ABSTRACT

Patients with sickle cell disease (SCD) can have recurrent episodes of vaso-occlusive crises, which are associated with severe pain. While opioids are the mainstay of analgesic therapy, in some patients, increasing opioid use results in continued and increasing pain. Many believe that this phenomenon results from opioid-induced tolerance or hyperalgesia or that SCD pain involves non-opioid-responsive mechanisms. Dexmedetomidine, a specific α_2-adrenoreceptor agonist, which has sedative and analgesic properties, reduces opioid requirements, and can facilitate opioid withdrawal in clinical settings. We hypothesized that dexmedetomidine would ameliorate the nociception phenotype of SCD mice. Townes and BERK SCD mice, strains known to have altered nociception phenotypes, were used in a crossover preclinical trial that measured nocifensive behavior before and after treatment with dexmedetomidine or vehicle. In a linear dose–effect relationship, over 60-min, dexmedetomidine, compared with vehicle, significantly increased hot plate latency in Townes and BERK mice ($P \leq 0.006$). In sickle, but not control mice, dexmedetomidine improved grip force, an indicator of muscle pain ($P=0.002$). As expected, dexmedetomidine had a sedative effect in sickle and control mice as it decreased wakefulness scores compared with vehicle (all $P<0.001$). Interestingly, the effects of dexmedetomidine on hot plate latency and wakefulness scores were different in sickle and control mice, i.e., dexmedetomidine-related increases in hotplate latency and decreases in wakefulness scores were significantly smaller in Townes sickle compared to control mice. In conclusion, these findings of beneficial effects of dexmedetomidine on the nociception phenotype in SCD mice might support the conduct of studies of dexmedetomidine in SCD patients.

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1. Introduction

Pain is the most common reason why sickle cell disease (SCD) patients seek medical attention and accounts for over 180,000 emergency room visits, 75,000 hospitalizations, and nearly one billion dollars in health care costs yearly (Ballas et al., 2012; Platt et al., 1991; Smith et al., 2008; Steiner and Miller, 2006; Yusuf et al., 2010). When patients are admitted for vaso-occlusive crises, even after several days of hospitalization some report little change in pain severity and after discharge, pain-related re-hospitalization rates remain high (Ballas and Lusardi, 2005; Brousseau et al., 2010). Opioids, the mainstay of SCD-pain therapy, are somewhat effective in alleviating symptoms during acute pain crises, but are often ineffective in treating chronic and neuropathic pain, which are also seen in SCD patients (Brandow et al., 2014; McNicol et al., 2013; Wilkie et al., 2010; Xu et al., 2014). In some patients, escalating doses of opioids can be associated with continued and increasing pain, which many believe results from tolerance, opioid-induced hyperalgesia, or reflects pain due to mechanisms unresponsive to opioid (Ballas et al., 2012; Brush, 2012). Most approaches to treat SCD-pain are based on expert opinion and observational studies rather than clinical trials (Field et al., 2009; Niscola et al., 2009) and often address symptoms rather than SCD-pain mechanisms (Field et al., 2009; Niscola et al., 2009). Therefore, new therapies are needed to improve the treatment of SCD pain.

Humanized SCD mice allow for the conduct of preclinical studies of therapies that might have a role in SCD pain. These animals display thermal, mechanical, and muscle hyperalgesia and sensitization of somatosensory fibers (Cain et al., 2012; Garrison et al., 2012; Hillery et al., 2011; Kenyon et al., 2015; Kohli et al., 2010; Vincent et al., 2013). Interestingly, this mechanical and thermal hyperalgesia is

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accentuated by hypoxia and reoxygenation, which suggest that the altered nocifensive phenotype in SCD mice could partially result from recurrent ischemia/reperfusion injury associated with vaso-occlusion (Cain et al., 2012; Hebbel, 2014). Therefore, SCD mice are valuable for the study of SCD-pain mechanisms and for the evaluation of novel approaches that might ameliorate ischemia/reperfusion injury and treat SCD-pain.

Animal studies support the investigation of dexmedetomidine, a specific α_2-adrenoreceptor agonist (Bol et al., 1999; Kamibayashi and Maze, 2000) in SCD. For example, in visceral pain models, the antinociceptive effects of dexmedetomidine are opioid-receptor-independent and are associated with increased nitric oxide availability (Rangel et al., 2014). In neuropathic pain, the antinociceptive effect of dexmedetomidine results from supraspinal facilitation of inhibitory postsynaptic currents and inhibition of sensory neurons (Funai et al., 2014). Lastly, in several models of organ ischemia/reperfusion injury, dexmedetomidine has been shown to have protective effects (Bell et al., 2012, 2014; Dong et al., 2014; Sahin et al., 2013; Yoshitomi et al., 2012). Therefore, given that ischemia/reperfusion injury underlies SCD complications and that dexmedetomidine has beneficial effects in those settings, one could argue that studies of dexmedetomidine in SCD are warranted. Here we examined the effect of dexmedetomidine in SCD and hypothesized that this α_2-adrenoreceptor agonist would ameliorate the nocifensive phenotype in SCD mice.

2. Materials and methods

The investigational protocol was approved by the Children's National Health System Institutional Animal Care and Use Committee and all experiments were conducted in compliance with the Guide for the Care and Use of Laboratory Animals, National Institutes of Health.

2.1. Animals

We examined the Townes [B6;129-*Hba*$^{tm1(HBA)Tow}$*Hbb*$^{tm2(HBG1,HBB*)Tow}$/*Hbb*$^{tm3(HBG1,HBB)Tow}$/J (Jackson Laboratory, Stock number 013071] (Hanna et al., 2007; Kenyon et al., 2015; Wu et al., 2006) and the BERK strains of humanized SCD mice [*Hba*^{tm1Paz} *Hbb*^{tm1Tow} Tg(HBA-HBBs) 41Paz/J, Stock number 003342] (Paszty et al., 1997). Townes sickle mice do not express mouse hemoglobin and carry mutations that incorporate human hemoglobin. One mutation is designed with the human hemoglobin α-gene (*Hba*$^{tm1(HBA)Tow}$, hα) and the second with a 9.7-kb DNA fragment that contains human $^{A}\gamma$-globin gene and sickle hemoglobin (*Hbb*$^{tm2(HBG1,HBB*)Tow}$, β^S). These animals (hα/hα::β^S/β^S), here referred to as Townes sickle mice, recapitulate several hematologic phenotypes of human SCD (anemia, reticulocytosis, leukocytosis, sickling) and have liver as well as kidney pathology (Hanna et al., 2007; Wu et al., 2006). Similarly, Townes control mice do not express mouse hemoglobin and carry mutations containing the human α-globin gene and fragments of the human hemoglobin gamma ($^{A}\gamma$) and human wild-type beta globin (*Hbb*$^{tm3(HBG1,HBB)Tow}$, β^A) genes (hα/hα::β^A/β^A) (Hanna et al., 2007; Wu et al., 2006).

In some experiments, we also examined another strain of SCD, the BERK sickle mice (Jackson Laboratory, Stock number 003342) (Paszty et al., 1997). These animals do not express any mouse hemoglobin and carry copies of a transgene [Tg(HBA-HBBs)41Paz] containing human *HBA1* (hemoglobin, alpha 1), *HBG2* (hemoglobin, gamma G, fetal component), *HBG1* (hemoglobin, gamma A, fetal component), *HBD* (hemoglobin, delta) and *HBB*^{S} (hemoglobin, beta, sickle allele) genes (Paszty et al., 1997). We used C57BL/6J as the control strain for BERK sickle mice due to the lack of availability of BERK control mice expressing normal human hemoglobin. Further, because of significant limitations on availability of BERK mice, only females were included in only some experiments in this study. Mice were housed in a temperature-controlled facility (21 °C) with a standard 12-h light–dark schedule. Mice from all genotypes were housed together in an attempt to control for estrous cycles. During any given experiment of nocifensive behaviors, a group of SCD and respective control mice were examined.

2.2. Study design and experimental protocol

The experimental design adhered to the suggested framework aimed at increasing the predictive value of preclinical trials (Landis et al., 2012). We conducted a randomized controlled crossover trial where all mice received a single subcutaneous injection of either vehicle (phosphate buffered saline) or various doses of dexmedetomidine (10, 25, 50, or 100 μg/kg) during each experiment. Measurements were obtained at baseline (24 h before) and at 30 and 60 min after drug administration. Between experiments, a minimum of 72-h drug-washout period was observed. In SCD mice, we evaluated nocifensive behavior (current vocalization threshold, hot plate latency, and grip force) and measured the wakefulness score both before and after injections. Experiments were performed between 9:00 a.m. and 02:00 p.m. in a quiet room with one animal present during interventions. One investigator administered all study drugs and another, who was unaware of the animals genotype or treatment received, obtained the outcome measurements. In order to avoid operator variability, the same investigator obtained given nocifensive behavior measurement for the entirety of the experiments.

2.3. Nocifensive behavior studies

Three cohorts of mice were used in this study. One cohort underwent hot plate latency followed by current threshold measurements, another underwent grip force evaluation, and the third was used for wakefulness scores.

2.3.1. Hot plate latency

In order to evaluate the effect of dexmedetomidine on response to noxious thermal stimuli, mice were placed on a hot plate (Harvard Apparatus, Holliston, MA) set at 55 °C and latency time for the display of pain-avoiding behaviors (jumping, stomping or repeated lifting or licking of hind or front paws) was measured. Once these behaviors were observed, mice were removed from the hot plate (Le Bars et al., 2001). In order to avoid injuries, animals were allowed to remain on the hot plate for a maximum of 30 s. In this crossover design, all animals received one injection of either dexmedetomidine (50 or 100 μg/kg) or vehicle in each of the four experiments.

2.3.2. Sensory nerve fiber evaluation – current vocalization threshold

In the same cohort of animals that underwent the hot plate test, we evaluated somatosensory fiber function using sine-wave electrical stimuli at different frequencies: 2000, 250, and 5 Hz that preferentially stimulate Aβ, Aδ, and C fibers respectively (Finkel et al., 2006, 2012; Kenyon et al., 2015; Koga et al., 2005). Briefly, sine-wave electrical stimuli generated by a neurostimulator (Neurotron, Inc, Baltimore, MD) and controlled by custom software were delivered to the mouse tail as previously described (Finkel et al., 2006, 2012; Spornick et al., 2011). Electrical stimuli (2000, 250, and 5 Hz) were delivered at increasing intensities for one second followed by a one-second stimulus-free interval (50% duty cycle). Between stimulations with different frequencies, there was a one-min rest period. The electrical stimulus amperage that elicited audible vocalization (nocifensive behavior endpoint) or the maximum amperage delivered at each frequency was recorded as the respective current threshold (Finkel et al., 2006, 2012; Spornick et al., 2011). Current thresholds for each frequency were determined by averaging five consecutive measurements and were obtained in

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