Targeted ablation of mesenteric projecting sympathetic neurons reduces the hemodynamic response to pain in conscious, spinal cord-transected rats

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Lujan HL, Palani G, Peduzzi JD, DiCarlo SE. Targeted ablation of mesenteric projecting sympathetic neurons reduces the hemodynamic response to pain in conscious, spinal cord-transected rats. Am J Physiol Regul Integr Comp Physiol 298: R1358–R1365, 2010. First published March 10, 2010; doi:10.1152/ajpregu.00755.2009.—Individuals with spinal cord injuries above thoracic level 6 (T6) experience episodic bouts of life-threatening hypertension as part of a condition termed autonomic dysreflexia (AD). The paroxysmal hypertension can be caused by a painful stimulus below the level of the injury. Targeted ablation of mesenteric projecting sympathetic neurons may reduce the severity of autonomic dysreflexia by reducing sympathetic activity. Therefore, cholera toxin B subunit (CTB) conjugated to saporin (SAP), a ribosomal inactivating protein that binds to and inactivates ribosomes, was injected into the celiac ganglia to test the hypothesis that targeted ablation of mesenteric projecting sympathetic neurons reduces the pressor response to pain in conscious, spinal cord-transected rats. Nine Sprague-Dawley male rats underwent a spinal cord transection between thoracic vertebrae 4 and 5. Following recovery (5 wk), all rats were instrumented with a radio telemetry device for recording arterial pressure and bilateral catheters in the gluteus maximus muscles for the infusion of hypertonic saline (hNaCl). Subsequently, the hemodynamic responses to intramuscular injection of hNaCl (100 μl and 250 μl, in random order) were determined. Following the experiments in the no celiac ganglia injected condition (NGI), rats received injections of CTB-SAP (n = 5) or CTB (n = 3) into the celiac ganglia. CTB-SAP rats, compared with NGI and CTB rats, had reduced pressor responses to hNaCl. Furthermore, the number of stained neurons in the celiac ganglia and spinal cord (segments T6–T12), was reduced in CTB-SAP rats. Thus, CTB-SAP retrogradely transported from the celiac ganglia is effective in ablating mesenteric projecting sympathetic neurons and reducing the pressor response to pain in spinal cord-transected rats.

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since lesions at spinal segment T₆ or above are required for the development of AD, we assessed spinal levels T₆ and T₇ for ablation of SPNs. To document that afferent function was not altered by SAP, we examined the dorsal root ganglia of spinal segments T₃–T₁₂. We studied conscious, chronically instrumented rats to negate the confounding effects of anesthetic agents and surgical trauma.

MATERIALS AND METHODS

Experimental procedures and protocols were reviewed and approved by the Animal Care and Use Committee of Wayne State University and adhered to the American Physiological Society’s Guiding Principles in the Care and Use of Animals. Nine adult spinal cord-transected Sprague-Dawley male rats were studied before celiac ganglia injection [no celiac ganglia injection (NGI)]. Subsequently, the rats were randomly divided into two groups: 1) celiac ganglia injection of CTB (n = 3) and 2) celiac ganglia injection of CTB-SAP (n = 5). One rat in the NGI condition did not survive the celiac ganglion injection procedure.

Surgical Procedures

All surgical procedures were performed using aseptic surgical techniques. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip), atropinized (0.05 mg/kg ip), intubated, and prepared for aseptic surgery. Supplemental doses of pentobarbital sodium (10–20 mg/kg ip) were administered if the rat regained the blink reflex or responded during the surgical procedures.

Spinal cord transection. After anesthesia was induced, the rats were intubated and positioned prone over a thoracic roll that slightly flexed the trunk. The fourth thoracic vertebra was exposed via a midline dorsal incision, and the spinous process and laminae were removed. Two ligatures (6-0 silk) were tightened around the underlying spinal cord between the T₅ and T₆ segments, and the spinal cord was completely transected by cutting between the ligatures with scissors (28). In this way, there was minimal bleeding. The completeness of the transection was confirmed by visual inspection of the lesion site. During the acute recovery period (~10 days), all rats were handled at least six times daily. During these periods, visual inspections and physical manipulations were performed to detect and prevent pressure sores. In addition, the urinary bladder was voided by manual compression, and all animals were weighed. After this acute recovery period, rats required only daily inspection, and the bladders did not require manual compression. In addition, body weight was recorded at least every other day to determine the overall health of the animals. Specifically, body weight on the day of the spinal cord transection averaged 424 ± 11 g. At the completion of the studies, the body weights of the spinal cord-transected rats averaged 399 ± 11 g. It is important to note that spinal cord-transected rats eat unassisted and move themselves around the cage with their forelimbs. In fact, rats with identical spinal cord transections have been studied after dynamic exercise (7). Specifically, spinal cord-transected rats had their lower bodies secured onto a small cart and “ran” on a motor-driven treadmill. The spinal cord-transected rats propelled themselves with their upper bodies at 9–12 m/min for 40 min without the use of adhesive stimuli (7).

At day 7 posttransection, the rats received a motor activity score using criteria described previously (52). The motor activity score was assessed by placing the animal on a paper-covered table and observing spontaneous motor activity for 1 min. Motor scores ranged from 0 to 5. A motor score of 5 indicates normal walking, whereas a score of 0 indicates no weight bearing or spontaneous voluntary movement in the hind limbs. All rats had a motor score of 0, which indicates no weight bearing. Upon completion of the studies, the site of the spinal transection was confirmed by autopsy. All rats were allowed to recover at least 5 wk.

Radiotelemetry implantation. Subsequently, the rats were anesthetized as described above and a telemetry device (model no. TA11PA-C40; Data Sciences International) was implanted in all rats as previously described (6, 7) for chronic, untethered measurements of arterial pressure and heart rate, and a catheter was placed in the intraperitoneal space for the infusion of fluids and drugs. Specifically, the transmitter body and the intraperitoneal catheter were placed in the intraperitoneal space through a ventral abdominal approach. The intraperitoneal catheter was exteriorized on the dorsal aspect of the neck. The pressure sensor of the telemetry device, located within the tip of a catheter, was inserted into the descending aorta via the left carotid artery. In addition, bilateral catheters were placed in the gluteus maximus muscles for the infusion of Na⁺Cl⁻. A minimum of 1 wk was allowed for recovery and for the animals to regain their presurgical weight. During the recovery period, the rats were handled, weighed, and acclimatized to the laboratory and investigators.

Experimental Procedures

Autonomic dysreflexia protocol. After the recovery period, conscious, unrestrained rats were studied in their home cages (~13,350 cm³) for all experiments. On the day of the experiment, rats were brought into the laboratory and allowed to adapt to the environment for approximately 1 h to ensure stable hemodynamic conditions (stabilization period). After the stabilization period, beat-by-beat, steady-state hemodynamic variables were recorded over 10 to 15 s. Subsequently, cardiac autonomic blockade was produced. Specifically, cardiac muscarinic-cholinergic receptor blockade was achieved by infusion of the nonspecific muscarinic-cholinergic receptor antagonist atropine methyl bromide (methylatropine 3 mg/kg), and cardiac β₁-adrenergic receptor blockade was achieved by infusion of the specific β₁-adrenergic receptor antagonist metoprolol (10 mg/kg) into the intraperitoneal catheter. This was done to eliminate the bradycardic response associated with AD since this response is not consistent (6, 7). The efficacy of cardiac autonomic blockade with intraperitoneal administration of these doses was previously determined (4). Subsequently, the heart rate and arterial pressure responses to 5% Na⁺Cl⁻ injected into the gluteus maximus muscle were determined (intervention period). Intramuscular injections of Na⁺Cl⁻ is an established model for examining pain mechanisms in both humans (49) and animals (3, 44, 45). The volumes of 100 and 250 µl (in random order with at least 20 min between injections) of Na⁺Cl⁻ were chosen because a volume of 250 µl injected into cat mesenteric muscle consistently yielded reliable results without producing muscle necrosis even after multiple injections (3, 44, 45). Intramuscular injection of Na⁺Cl⁻ produced robust pressor responses in spinal cord-transected rats (Fig. 1). The entire data collection took ~2 h. At the end of the experiment, the rats were returned to their housing facilities.

Autonomic dysreflexia protocol postceliac ganglia injections. Following the NGI experiment, rats were randomly divided into two groups and received injections of CTB-SAP (n = 5) or CTB (n = 3) into the celiac ganglia. The animals were anesthetized as described above, and the celiac ganglion was approached via a ventral abdominal incision. The intestines were moved superiorly in the abdominal cavity, exposing the aorta, superior mesenteric artery, and celiac artery. The celiac ganglion was located on the descending aorta at the branch points between the celiac and superior mesenteric arteries. Nine microliters of CTB subunit (1 mg CTB dissolved in 200 µl of distilled water; cat. no. 103-B; List Biological Laboratories, Campbell, CA) or 9 µl of CTB conjugated with SAP (2.5 mg/ml; cat. no. IT-14; Advanced Targeting Systems, San Diego, CA) were mixed with 1 µl of 3% Evans blue dye. The purpose of the Evans blue dye was to visualize the injectate (CTB and SAP are colorless), assuring localization within the ganglia. All injections were confined within the celiac ganglia. The CTB/Evans blue dye or CTB-SAP/Evans blue dye solutions were pressure-injected with mineral oil into the ganglia.
Ganglia were cryoprotected in increasing concentrations of sucrose. Spinal cords and ganglia are concentrated in these segments (51). Spinal cords and ganglia from all rats were removed and postfixed intact in 4% formaldehyde for 3 days at room temperature on a shaker. After postfixation, the spinal cords were removed and divided into single segments T5–T12 were obtained because SPNs projecting to the celiac ganglia injection (NGI), segments T5–T12 were obtained because SPNs projecting to the celiac ganglia (50). The pressor response to intramuscular injection of hypertonic saline was notably lower in the rat with celiac ganglion injection (CTB-SAP) revealed no neurons (see Fig. 4).

**Data Analysis**

All data are from nine rats before celiac ganglia injection (NGI): five rats in the CTB-SAP condition and three rats in the CTB condition (one CTB rat did not survive the final protocol). All recordings were sampled at 2 kHz, and the data were expressed as means ± SE. All data for the stabilization period were the average of every beat during the last 10–15 s of the period. For the intervention period, data were the average of every beat during the 10–15 s around the peak response. Two separate one-factor ANOVAs (1 before and 1 after cardiac autonomic blockade) were used to compare resting mean arterial pressure and heart rate (Table 1). Two separate two-factor ANOVAs with repeated measures (NGICTB vs. CTB and NGICTB-SAP vs. CTB-SAP) and the post hoc Holm-Sidak method were used to compare resting mean arterial pressure and heart rate. ANOVAs with repeated measures (NGICTB vs. CTB and NGICTB-SAP vs. CTB-SAP) and the post hoc Holm-Sidak method were used to compare resting mean arterial pressure and heart rate.
compare the pressor response to 100 and 250 µl hNa⁺Cl⁻ in the NGI, CTB, and CTB-SAP groups (Fig. 2). Finally, a one-factor ANOVA was used to compare neuronal number and soma area between the NGI, CTB, and CTB-SAP groups (Fig. 3).

RESULTS

Table 1 presents mean arterial pressure and heart rate at rest and before and after cardiac autonomic blockade in the three groups of rats: 1) NGI, 2) CTB injected into the celiac ganglia, and 3) CTB-SAP injected into the celiac ganglia. Resting mean arterial pressure and heart rate before and after blockade were not different between the three groups.

Figure 2 presents the change in mean arterial pressure in response to 100 µl and 250 µl of hNa⁺Cl⁻ injected into the gluteus maximus muscle in the NGI, CTB, and CTB-SAP conditions. The control data for the CTB and CTB-SAP, rats are presented separately. Specifically, the three animals that received CTB were matched with their response before injection (NGICTB). The five animals that received CTB-SAP were matched with their response before injection (NGICTB-SAP). The change in mean arterial pressure in response to 100 µl or 250 µl of hNa⁺Cl⁻ was not different between the NGI and CTB groups (F = 0.154, df = 1). However, the pressor response to 250 µl was significantly greater than the response to 100 µl across groups (F = 37.896, df = 1). In sharp contrast, the arterial pressure response to both 100 µl and 250 µl of hNa⁺Cl⁻ were significantly lower in the CTB-SAP group documenting an attenuated AD (Fig. 2). Furthermore, the pressor response to 250 µl was significantly greater than the response to 100 µl across groups (F = 52.7, df = 1).

Figure 3 presents neuronal number (A), average soma area per neuron (B), and cresyl violet-stained celiac neurons (C) from rats that had NGI or CTB or CTB-SAP injected into the celiac ganglia. Counts of celiac neurons in the CTB-SAP group showed a significant reduction in the number of neurons compared with both the NGI and CTB groups (1,275 ± 382 vs. 7,284 ± 784 and 6,775 ± 414, respectively). These results are consistent with Fig. 3C showing many celiac neurons in the NGI and CTB groups with few neurons in the CTB-SAP group. However, of the 2,711 neurons analyzed, the soma area (Fig. 3B) was not different between the three groups (NGI: 358 ± 9, CTB: 482 ± 22, and CTB-SAP: 430 ± 37 microns²).

Figure 4 presents CTB-immunoreactive neurons of the T6–T7 spinal cord from rats that had CTB or CTB-SAP injected into the celiac ganglia. CTB-immunoreactive SPNs were found on both sides of the column of the T6–T7 spinal cord in CTB rats (Fig. 4A). However, virtually all of the CTB-immunoreactive SPNs were eliminated in the CTB-SAP group (Fig. 4B). Control slides (without primary antibody) did not have labeled cells.

Figure 5 presents cresyl violet-stained dorsal root ganglia neurons from rats that had CTB or CTB-SAP injected into the celiac ganglia. Rats with celiac ganglion injections of CTB-SAP did not have afferents disrupted since neurons within the dorsal root ganglia were not affected, suggesting that afferent pathways remained functional.

DISCUSSION

In this study, we tested the hypothesis that celiac ganglion injection of CTB-SAP would reduce the hemodynamic responses to pain (AD) in spinal cord-transected rats. The major findings of this study include: 1) CTB-SAP rats had a reduced blood pressure response to intramuscular injection of hNa⁺Cl⁻ (Figs. 1 and 2), and 2) associated with the reduced pressor response to hNa⁺Cl⁻ was a reduction in the number and/or area of celiac postganglionic neurons and celiac projecting SPNs (Figs. 3 and 4) without affecting afferent neurons (Fig. 5). Since AD is caused by a massive sympathetic discharge triggered by the stimulus originating below the level of the spinal cord injury (20), these data suggest that CTB-SAP reduced the sympathetic response to a painful stimulus below the level of the lesion in spinal cord-transected rats.

Autonomic dysreflexia occurs in as many as 85% of individuals with spinal cord injuries above T6 and is characterized by severe hypertension, sweating, dizziness, nausea, and severe headaches. AD may be caused by stimulation of the skin, distension of the urinary bladder or colon, pain, and muscle spasms. The afferent stimulation below the level of the injury results in massive sympathetic activity that causes vasoconstriction of most vascular beds below the injury and baroreflex-mediated bradycardia due to parasympathetic activation and sympathetic withdrawal above the lesion with resultant vasodilatation that mediates headaches and skin flushing. To prevent the baroreflex-mediated bradycardia, which has been documented to be inconsistent (6, 7), we performed cardiac autonomic blockade. We were interested in blocking the massive sympathetic activity to the mesenteric vasculature and cardiac autonomic blockade has no effect on this response.

Reductions in sympathetic responses are clinically important because excessive sympathetic responses are responsible for, and/or contribute to, the morbidity and mortality associated with many cardiovascular disorders. For example, the mechanisms mediating several forms of life-threatening hypertension involve excess sympathetic activity. Sympathetic activity increases cardiac output (heart rate and stroke volume) and vascular resistance as well as the release of vasoactive substances leading to elevations in blood pressure. Accordingly, reducing sympathetic activity and/or blocking the sympathetic
responses to stimuli are the first-line therapy for many hypertensive disorders. For example, β-adrenergic receptor antagonists are the first-line therapy for hypertension. However, despite their favorable effects, adverse complications (due to generalized sympathoinhibition; e.g., fatigue, impotence) limit compliance to these treatments. For example, the Medical Research Council trial (35) on hypertensive patients documented that for every myocardial infarction or stroke prevented by β-adrenergic receptor antagonists, three patients withdrew from the study secondary to impotence and another seven withdrew because of fatigue (37). Targeted, celiac ganglion injection of CTB-SAP may overcome these issues because celiac ganglion injection of CTB-SAP selectively reduces sympathetic activity to the mesenteric vasculature, avoiding generalized sympathoinhibition. Thus, this procedure should avoid limitations of medical therapy, such as incomplete compliance due to medical complications.

It is important to note that sympathectomy (ganglion ablation) is markedly different from targeted ablation of celiac sympathetic pre- and postganglionic neurons. Sympathectomy ablates fibers passing through the ganglia, disrupting afferent signals as well as efferent fibers ascending and descending within the sympathetic chain. In this context, rats with celiac ganglion injections of CTB-SAP did not have afferents disrupted, since neurons within the dorsal root ganglia were not affected (Fig. 5), suggesting that afferent pathways remained functional. This is important because many biological functions, for example the defecation reflex, are initiated by afferent stimuli and are mediated, in part, by spinal reflexes. Individuals with spinal injuries can take advantage of this reflex loop by using digital rectal stimulation to assist with defecation and other biological functions. However, additional studies will be required to further characterize this new procedure.

In addition, sympathectomy largely prevents norepinephrine release (possibly leading to denervation supersensitivity). Thus, there is no way to grade the level of sympathetic denervation. In sharp contrast, with celiac injections of CTB-SAP, it may be possible to adjust the dosage to partially denervate targets to desirable levels. Finally, this new method provides an additional technique to selectively denervate sympathetic control to the vasculature providing options for susceptible individuals.

**Clinical Implications**

Prior to World War II, 80% of individuals with spinal cord injury died within 3 yr of the injury. However, with the advent of antibiotic drugs and advancements in acute care and reha-
bilitation, the life expectancy of individuals with spinal cord injury has increased to near that for able-bodied individuals. Importantly, cardiovascular disease is now a leading cause of death and morbidity for individuals with spinal cord injuries (12). Autonomic dysreflexia may be a contributing factor since the long-term consequence of repeated episodes of severe hypertension has yet to be determined. However, it is well known that increased arterial pressure variability is a significant cardiovascular disease risk factor (9). Thus, interventions designed to reduce episodic bouts of hypertension may prevent end-organ damage, cerebral and subarachnoid hemorrhage, seizures, and renal failure and may prevent death.

It is important to note that the hypertension associated with AD is markedly underrecognized (10). This is a serious concern, because a continuous, strong, graded, independent, and etiologically significant relationship between elevated blood pressure and cardiovascular and cerebrovascular risk has been described (50). Thus, early intervention for all individuals with hypertension is recommended based on studies documenting that antihypertensive therapy reduces mortality and ameliorates symptoms of hypertension in individuals with accelerated hypertension as well as individuals with so-called benign hypertension. These results suggest that reducing the hemodynamic response to AD may have long-term beneficial consequences in individuals with spinal cord injury.

In addition, individuals with spinal cord injuries have distinct hemodynamic responses to a variety of activities of daily living. For example, it is well established that individuals with midthoracic cord injury have elevated heart rates and lower stroke volumes at rest and during activity than able-bodied individuals (16). Similarly, rats with midthoracic spinal cord injury have elevated heart rates (Table 1 and Refs. 21, 31, and 33), as well as increased cardiac sympathetic tonus (28, 46). Numerous studies have documented that an elevated heart rate is a strong risk factor for the development of cardiovascular disease (18, 42). Furthermore, elevated cardiac sympathetic activity is responsible for, and/or contributes to, the morbidity and mortality associated with many cardiovascular disorders. Thus, reducing cardiac sympathetic tonus with stellate ganglia injection of CTB-SAP may reduce the incidence of cardiovas-

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**Fig. 4.** CTB-immunoreactive neurons of the T6–T7 spinal cord from rats that had CTB (A) or CTB-SAP (B) injected into the celiac ganglia. CTB-immunoreactive sympathetic preganglionic neurons (SPNs) were found on both sides of the column of the T6 and T7 spinal cord in CTB rats (A). However, virtually all of the CTB-immunoreactive SPNs were eliminated in the CTB-SAP group (B). Scale bar (bottom right) = 25 μm.

**Fig. 5.** Cresyl violet-stained neurons of the dorsal root ganglia from rats that had CTB (A) or CTB-SAP (B) injected into the celiac ganglia. It is clear that CTB-SAP did not alter neurons within the dorsal root ganglia. Scale bar (bottom right) = 25 μm.
cular disorders in the spinal cord injury population (8, 28, 29, 48). This hypothesis merits future investigation.

Limitations

Although some investigators have raised questions with preparations where a common carotid artery (CCA) is ligated due to theoretical concerns about central ischemia and/or loss of a baroreceptor station, we have used this procedure for many years and do not believe it is a concern. Specifically, in an extensive evaluation of rodent models of cerebral ischemia, Ginsberg and Busto (15) concluded that unilateral CCA ligation in rats leaves the cerebral energy state unchanged. Although Levine and Payan (23) first observed that ~20% of Mongolian gerbils (Meriones unguiculatus) subjected to unilateral CCA ligation developed severe neurologic signs and died within 2 days; subsequent histologic studies revealed an absence of the expected posterior communicating arteries that, in rats, connect the carotid and vertebrobasilar arterial systems (24). Thus, concerns regarding central ischemia are unwarranted.

Regarding baroreceptor denervation, blockade of the left carotid sinus did not alter the reflex control of the circulation, which led the authors to suggest the existence of a central communication between the two carotid sinuses (1). Furthermore, Ciriello et al. (5) have shown that the afferents from the carotid and aortic baroreceptors converge to the same areas in the central nervous system. It is possible that because of the lack of information from one carotid baroreceptor, the responses to changes in pressure at the aortic baroreceptors increase. Finally, over 4–7 days after bilateral carotid sinus denervation, the strength of control of both peripheral resistance and atria rate, as well as mean arterial pressure, returned to the levels observed before denervation (40). Considering previous studies, as well as our experience with this procedure over several years, we do not believe that ligation of a single CCA affects the neural control of the circulation.

In conclusion, the results of this study show that CTB-SAP retrogradely transported from the celiac ganglia is effective at ablating sympathetic neurons innervating the mesenteric vasculature and reducing the hemodynamic response to intramuscular hNa⁺Cl⁻. This new procedure may become an option for individuals experiencing AD especially when compliance with pharmacological management is low due to the expense, forgetfulness, and the episodic nature of the hypertension.

Perspectives and Significance

Since 1914, members of the medical community have used celiac plexus blockade with a combination of steroid and anesthetic solutions to temporarily interrupt nociception stimuli from the pancreas in individuals with abdominal pain associated with chronic pancreatitis and advanced pancreatic cancer (19). Subsequently, permanent destruction of celiac ganglia neurons using a phenol- or alcohol-based solution was introduced for individuals with severe pain from intra-abdominal malignancies. These procedures are typically performed by anesthesiologists, interventional radiologists, and surgeons using a variety of percutaneous or intraoperative techniques (13, 25, 36, 53). Currently, with the development of the linear array echo endoscope, endosonographers easily localize and directly deliver anesthetic agents to the celiac plexus (14).

Since it has become easy to localize and directly deliver agents into the celiac plexus (41), celiac ganglia injections of CTB-SAP may be effective for conditions associated with excess sympathetic activity. However, additional studies are required to further characterize the physiological responses to this procedure and determine whether this new approach is safe and efficacious for the treatment of conditions associated with excess sympathetic activity. For example, the optimal dose along with correlations between the amount of neuronal destruction with CTB-SAP and the reduction in the pressor response to painful stimuli merits investigation. Careful analysis of potential gastrointestinal or urogenital effect must be conducted as well as the determination of whether targeted ablation of mesenteric projecting sympathetic neurons causes any further functional deficit.

GRANTS

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DISCLOSURES

No conflicts of interest are declared by the authors.

REFERENCES

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