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A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD)

Eugene G. Lipov [a,], Jaydeep R. Joshi [a], Sarah Sanders [a], Konstantin V. Slavin [b]

[a] Advanced Pain Centers S.C., 2260 W. Higgins Rd., Ste. 101, Hoffman Estates, IL 60169, United States
[b] Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL, United States

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The mechanism of action of the stellate ganglion block (SGB) is still uncertain; however it has been used successfully in treatment of chronic regional pain syndrome (CRPS) for many years. Our new insights in to the mechanism of action of the stellate ganglion block were first reported in 2007 in our publication detailing the control of hot flashes with the use of stellate ganglion blockade. We have demonstrated very significant results in the treatment of hot flashes and our most recent application of this block has been for the treatment of posttraumatic stress disorder (PTSD).

Stellate ganglion has been demonstrated to have second and third order neurons connections with the central nervous system nuclei that modulate body temperature, neuropathic pain, the manifestations of PTSD, and many other areas.

We believe that the commonality between the CRPS, HF and PTSD is the trigger of increased nerve growth factor (NGF) leading to the increase in brain norepinephrine (NR), which in turn is affected by the SGB leading to a prolonged reduction of NGF and eventually a decrease in NR. This, in turn, leads to a reduction or elimination of many of the symptoms of CRPS, Hot flashes, and PTSD.

Hypothesis

Stellate ganglion block (SGB) is a selective sympathetic block that influences ipsilateral head, neck, upper extremity, and the upper part of the thorax by temporarily blocking the sympathetic out flow to those regions. It has been used for at least 60 years as a treatment of migraines, atypical facial pain, upper extremity pain, and complex regional pain syndrome. In Japan, the stellate ganglion block has a much wider range of indications and is used for many systemic diseases including diseases of the immune and endocrine systems [1].

The mechanism of action of the stellate ganglion block is not completely understood, but has been described as involving peripheral vasodilatation, resulting from the neural inhibition in the ganglion's sphere of innervation [1]. However, the wide ranges of conditions that are known to respond favorably to stellate ganglion block suggest that its effectiveness may involve a far more complicated mechanism of action than a transient increase in blood flow. We have found that stellate ganglion block is effective in the treatment of hot flashes in postmenopausal women [2], as well as those with estrogen depletion resulting from breast cancer treatment [3,4].

We also recently reported that SGB has been effective for the treatment of PTSD on at least one patient [5]. Since that report, eight other PTSD patients have been treated successfully with this method (unpublished results).

Clearly above reports cannot be explained by the conventional explanation of the effect of SGB. Better understanding of sympathetic neuroanatomy via anatomical labeling techniques is starting to support explanations of the extensive effects of SGB for treatment of hot flashes, PTSD, and neuropathic pain. In the course of mapping the sympathetic nervous system to the related regions of the cerebral cortex, Westerhaus and Loewy used pseudorabies virus injections to identify connections of the stellate ganglion [6]. Pseudorabies virus allows identification of neural pathway connections that are 2–3 synapses from the point of injection of the virus. In this manner, the use of pseudorabies virus injection is used to identify cortical areas connected to the stellate ganglion. Early labeling was found in the hypothalamus and central nucleus of the amygdala. With slightly longer time labeling was found in lateral, basolateral, and medial amygdala. After 6–8 days, injections of the stellate ganglion produced extensive transneuronal labeling in the infralimbic, insular, and ventromedial temporal cortical regions (Fig. 1).

These data provides objective, anatomical support for the stellate ganglion interaction with several key structures known to modulate core body temperature, CRPS and PTSD. The hot

Corresponding author. Tel.: +1 847 742 8596; fax: +1 847 742 5135.
E-mail address: elipovmd@aol.com (E.G. Lipov).

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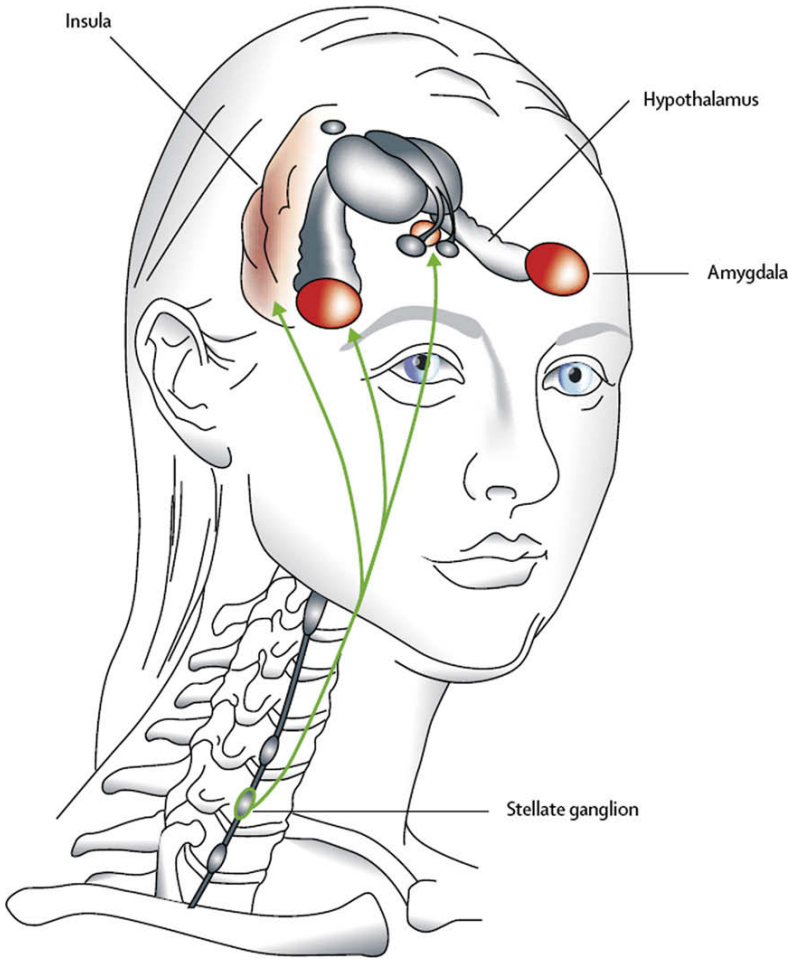

Fig. 1. These neurological connections were extensively discussed in our publication in 2007 [7].

flashes and PTSD are well known to be mediated in the brain. Most recently, CRPS has been added to this list, where Dr. Bogdak recognized CRPS as a central phenomenon [8]. Another investigative tool that has supported our hypothesis is functional magnetic resonance imaging (fMRI). It is widely used to study the operational organization of the human brain. The fMRI findings are consistent with the known aberrant neurologic states and provide further objective evidence of the structures involved. The following is a brief description of some of the findings with fMRI.

The insular cortex is activated during a hot flash [9], during mechanical hyperesthesia with CRPS [10], and in PTSD [11]. There is also an exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder [12]. Since CRPS and PTSD seem to be mediated at least in part via insular cortex one would anticipate that both conditions may occur simultaneously or one may lead to the other. One such report exists, where a Vietnam veteran had a recurrence of PTSD symptoms and simultaneous onset of CRPS in the leg, the authors felt both conditions has a common supraspinal mechanism [13].

Estrogen decrease leads to anxiety and depression [14], symptoms similar to PTSD

Our interpretation of the above is that neurological connections from the sympathetic ganglion to the brain structures exist and that those areas of connections are known to function during the pathological states discussed. A further step in the elucidation of the mechanism of the stellate ganglion blockade phenomena is the neurobiological understanding of the effect. We believe the unifying explanation is the change in nerve growth factor (NGF) eventually leading to an increase in brain norepinephrine (NR) and finally leading to pathologic states, with the SGB reducing the concentration of both NGF and NR and deactivating intracerebral pathologic states.

Evidence of nerve growth factor increase in pathologic states

Nerve growth factor (NGF) is the best characterized member of the neurotrophin family, which is involved in a variety of signaling events such as cell differentiation and survival, growth cessation, and apoptosis of neurons [15]. Its levels have been evaluated and seem to change with the conditions discussed. Studies indicate that estrogen reduces NGF protein content in sympathetic vascular targets [16].

Reciprocal regulation of estrogen and NGF receptors was noted in C12 cells [17]. NGF levels are known to increase with chronic stress [18]. NGF is also known to elevate immediately prior to the first parachute jump [19], thus demonstrating a NGF connection with stress and possibly PTSD. Anti-NGF antibodies can reduce CRPS symptoms [20]. In addition, NGF administration can lead to hyperesthesia [21].

Evidence of NGF increase leading to retrograde transport and eventually sprouting

NGF increase leads to retrograde transport from the intracerebral site to the stellate ganglion [22] (Fig. 2). Furthermore, a NGF increase in the stellate ganglion leads to sprouting and new nerve growth at the end terminals [23]. Additional collaborating evidence for new neurologic growth was described in ovariectomized rats. A 59% increase in sprouting of the sympathetic fibers in the uterus was seen [24].

Evidence of sprouting leading to brain norepinephrine (NE) increase and the NE leading to the pathologic states

Sprouting further leads to increased norepinephrine (NE) (Fig. 3). Brain infusion of NGF in rats leads to NE increase [25]. Direct evidence that NE is involved in hot flashes, CRPS, and PTSD can be found in the literature. Injection of NE in the brain leads to hot flashes in rats [26]. Injection of the alpha 2-adrenergic antagonist yohimbine leads to an increase in norepinephrine brain levels and provokes hot flashes in symptomatic women, an effect that is reduced by clonidine, an alpha 2 agonist [27]. Peripheral measurement of NE is consistent with the model of increased hot flashes [28]. An increase in NE leads to hyperesthesia, one of the main features in CRPS [29]. Urine levels of NE are known to increase in PTSD [30].

Evidence for local anesthetic effect on the NGF and the sympathetic nerve sprouting

The final part of this hypothesis is the evidence that the application of local anesthetic to a sympathetic ganglion leads to the reduction of NGF. Nerve growth factor having been the original trigger starting the cascade of events leading to the abnormal conditions presented. Local anesthetic application to the stellate ganglion nerve tissue reduces NGF that is essential for maintenance of sprouting [31]. The NGF decrease leads to dying of new nerve outgrowth and sprouting [32] (Fig. 4).

Conclusion

Based on the evidence summarized, we believe that CRPS, hot flashes and PTSD are centrally mediated, where a relevant insult leads to increase in NGF levels which starts a cascade that leads to sympathetic sprouting, which further increases brain norepinephrine, which finally leads to the clinical conditions in described in this article. Reversal of this cascade occurs by application of the local anesthetic to the stellate ganglion, which reduces NGF, which reduces sympathetic sprouting, leading to the reduction of the brain norepinephrine, which finally results in resolution of symptoms of CRPS, hot flashes and PTSD. This hypothesis provides a plausible explanation for the prolonged effect of the local anesthetic markedly beyond the length of the half life expected by the pharmacokinetics of the local anesthetic (LA). It also provides a novel and logical explanation of the prolonged effect of the LA in CRPS, a phenomina still poorly understood.

Of course, further work regarding this mechanism is needed to confirm this hypothesis, though much of other work as well as our publications support this hypothesis. We believe the time spent further researching this unified hypothesis is very appropriate as a significant increase in the understanding of the underlying mechanisms of CRPS, hot flashes, and PTSD would occur. As this hypothesis is further confirmed, we believe the ramifications of this new understanding of these three conditions will have profound implications. It may lead to a paradigm shift in not only the fundamental understanding of these conditions, but a change in treatment as

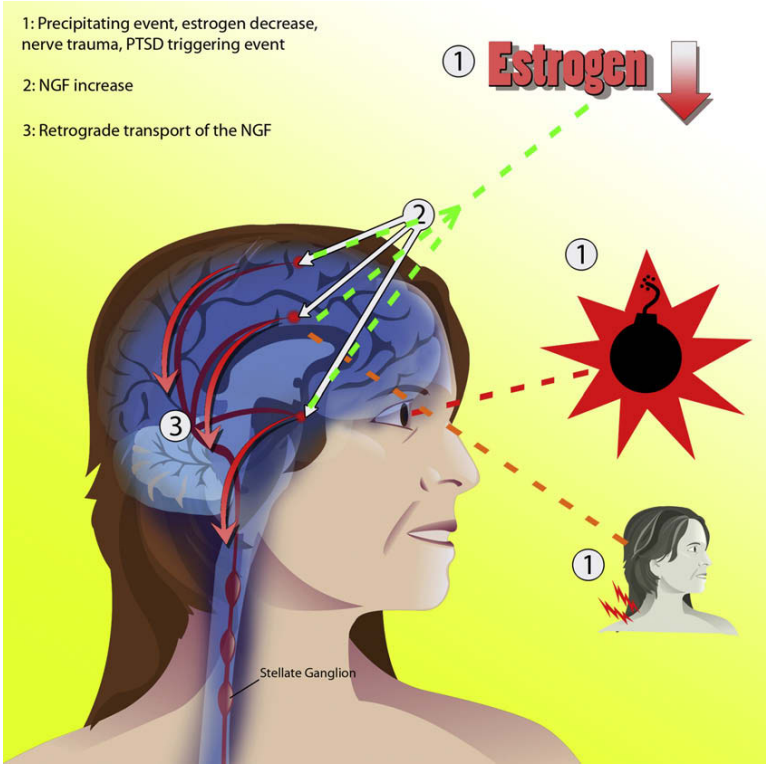

Fig. 2. Onset of the cascade of events from the precipitating event to NGF increase to retrograde transport of the NGF.

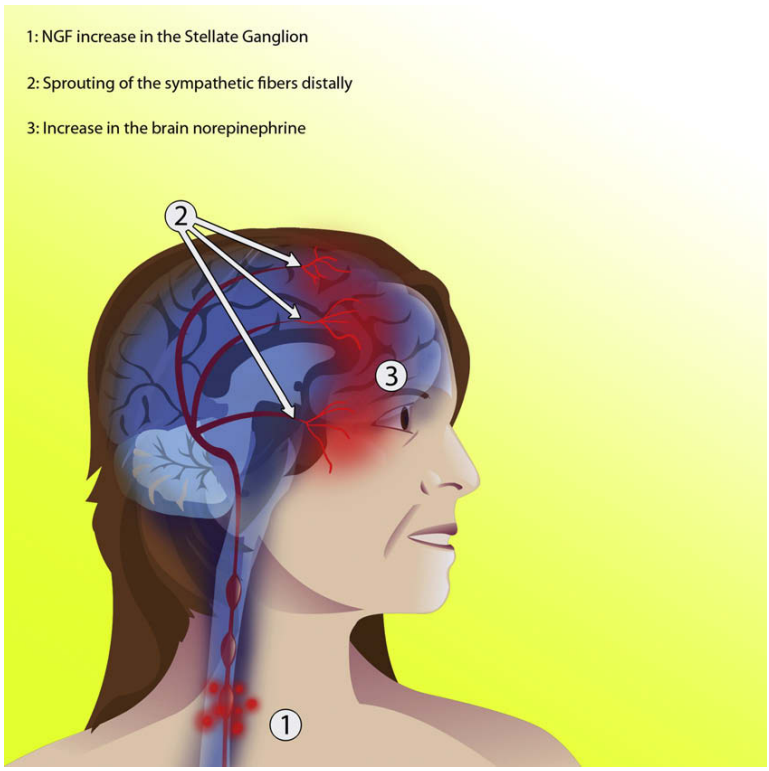

Fig. 3. Onset of symptoms hallmarked by NGF increase in the stellate ganglion followed by sprouting of the sympathetic fibers distally followed by increase in the brain norepinephrine.

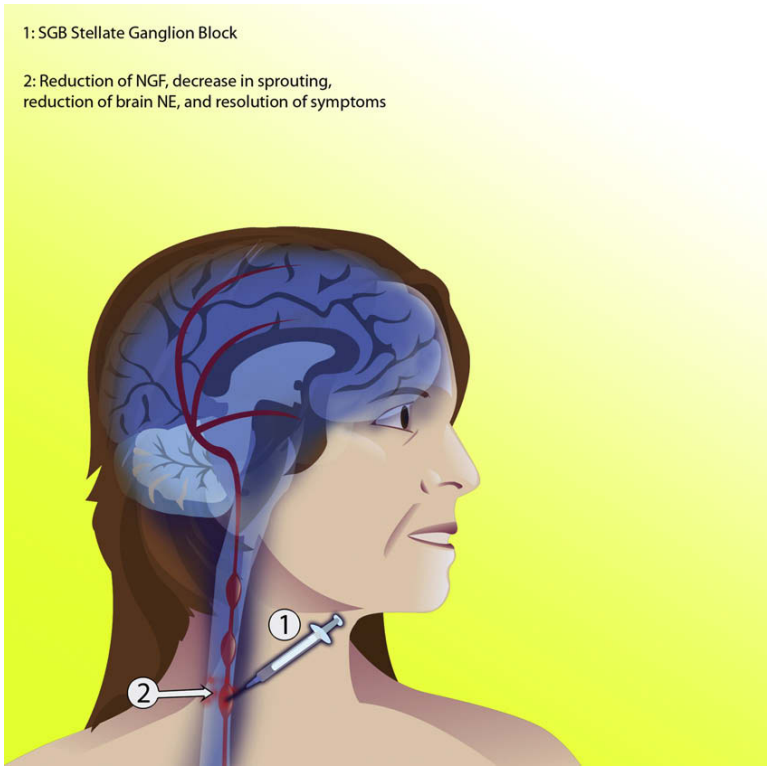

Fig. 4. Treatment seen as a result of stellate ganglion block resulting in reduction of NGF resulting in a decrease in sprouting resulting in reduction of brain NE and finally and resolution of symptoms.

well. In that light, this hypothesis may open new doorways and be responsible for the relief of other symptoms responsive to the stellate ganglion block.

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