

# A review of the role and mechanisms of action of baclofen in the management of central hyperthermia

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## ABSTRACT

Baclofen was previously known for its efficacy to treat spasticity but this agent has been studied and reported to have several other uses including its role in central hyperthermia. Central hyperthermia is associated with increased morbidity, mortality, and the impact of neuronal damage on the central nervous system. Until now there is no established guideline for the management of central hyperthermia which generally does not respond to standard antipyretic therapy. In this literature review, we will discuss the basic concepts of central hyperthermia and the role and mechanism of action of baclofen as an option for central hyperthermia therapy.

**Keywords:** baclofen, central hyperthermia, management, mechanism

## INTRODUCTION

Central hyperthermia is a condition of high fever with rapid onset of events and marked fluctuation which carries a significant mortality rate [1]. Central hyperthermia can be found in several conditions including hemorrhagic and ischemic stroke especially in the brain stem region. Central fever is still a diagnosis of exclusion so a thorough investigation of infection which is the most common cause of fever and complication of stroke must be carried out in an integrated manner. There is no strong evidence for definitive management of central hyperthermia to date, but several case studies report the successful treatment of central hyperthermia using baclofen [2].

## THE INCIDENCE AND PATHOPHYSIOLOGY OF CENTRAL HYPERTHERMIA

Fever is a very common complication of stroke and other medical conditions associated with a poorer prognosis. Fever is generally related to infection due to the susceptibility of stroke patients

and other medical conditions to various complications such as aspiration pneumonia, urinary tract infections, and pressure sores. Fever in the absence of detectable infection that is assumed to be of central origin was found in approximately 33% of stroke patients in a prospective study [1]. Characteristics of central hyperthermia include a rapid onset of high-temperature elevation, significant temperature fluctuations, and high mortality.

Brain stem hemorrhagic and occlusion stroke can trigger central hyperthermia. Intracerebral hemorrhage in the brain stem has a higher incidence of central fever than cerebral infarction. Most stroke patients with central fever have an increase in temperature to 39°C within 1 day [3], however, central fever may be non-persistent and may subside within 96 hours in 90% of stroke patients. Central fever is quite rare in the subacute phase of stroke.

Central fever is a diagnosis of exclusion. The diagnosis of central hyperthermia in stroke cases must meet the following criteria [2]: no initiating infection or fever at least 1 week before stroke onset; high fever (>39°C) developing within 24 hours

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of stroke onset; the results of the fever investigation due to infection are negative.

Body temperature is strictly regulated in humans as high as 37°C. Several physiological mechanisms are involved in temperature homeostasis, all of which are coordinated through the hypothalamus. Heat production in normal adults is through shivering, increase metabolic rate, and less often through sympathetically mediated nonshivering thermogenesis. It has been suggested that nonshivering thermogenesis may play an important role in quadriplegic patients with severe brainstem infarction who have long-term central hyperthermia [4].

Brown adipose tissue (BAT) is the main effector of nonshivering thermogenesis in humans by transferring energy from food to heat. The central pathways controlling thermogenesis, thermoregulation, and BAT innervation are complex [5]. The preoptic chiasm/anterior hypothalamic nucleus (POAH) is considered the body temperature control center. Cooling the area activates BAT, whereas warming suppresses BAT activation and nonshivering thermogenesis. Efferent from POAH is a gamma-aminobutyric acid (GABA) inhibitor to reach the ventromedial nucleus of the hypothalamus (VMN).

Signals from the VMN probably pass through the periaqueductal gray and are further mediated via “inhibition centers” in the lower mesencephalon [6]. Output from the inhibitory center can reach the raphe nucleus and release GABA in that area. Thermoregulatory signals are then mediated by the inferior olivary nucleus and intermediolateral neurons associated with the sympathetic chain. The sympathetic chain then controls BAT for nonshivering thermogenesis. The mechanism is tonically inhibited by thermoneutrality, but the inhibition is released under cold conditions. Based on this model in experimental animal studies, transection between the pons and medulla will eliminate descending inhibitory signals (GABA). Decerebration can release this inhibition and cause an excessive increase in body temperature due to increased BAT thermogenesis. This may explain hyperthermia in patients with bilateral pontine infarction [4].

The mechanism of central fever in neurointensive care units is not known for certain, but several mechanisms have been suggested. Inflammatory markers that cause fever can be triggered by extreme physiological stress in acute neurologic injury. Brain injury can also disrupt the mesencephalic-diencephalic mechanisms responsible for the inhibition of thermogenesis. Monocytes and macrophages produce cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF-alpha), which act on the organum vasculosum of laminae terminalis. These will trigger the release of prostaglandin E2 (PGE2) through the activation of the cyclooxygenase

(COX-2) enzyme. PGE2 acts on the preoptic area of the hypothalamus and causes an increase in the hypothalamic starting point so that there is an increase in body temperature [7].

Systemic pyrogens such as IL-1 appear to enter the brain in areas where the blood-brain barrier is incomplete (circumventricular organs) and act on the preoptic area to induce fever. Various neurologic events accompanied by fever are influenced by this pathway. Direct hemotoxic damage to the thermoregulatory center in the preoptic area, interacts with tonic inhibitory input from the lower mesencephalon that generally suppresses thermogenesis, and stimulation of prostaglandin production causes an increase in baseline temperature, resulting in central fever. Central fever is thought to result from damage to the hypothalamus, mesencephalon, or pons, and is increased by increased sympathetic activity, ventricular opening, frontal lobe damage, physical distortion, diffuse axonal injury, or toxic blood metabolites [8].

Post-traumatic hyperthermia, also known as neurogenic fever, is another common cause of fever. Stimulation studies suggest that the mechanism of the condition involves an imbalance between the hypothalamus and various temperature-regulating centers in the brainstem and spinal cord [9]. Won and Lin in their study using rabbits found that inhibition of the 5-hydroxytryptamine receptor in the anterior hypothalamus increases heat production and decreases heat loss thereby triggering hyperthermia [10]. The presumed mechanisms involve increased metabolic rate, increased carbon dioxide production, decreased cerebral blood flow, acidosis, exacerbation of cerebral edema, excitotoxic neurotransmitters release, and breakdown of the blood-brain barrier.

## MANAGEMENT OF CENTRAL HYPERTHERMIA

The long-term pharmacological management of central hyperthermia is still difficult to study due to the high mortality and poor prognosis in these cases. Fever control is very important because of its negative impact on the brain. Management of central hyperthermia includes a multimodal approach but there are still no definitive guidelines to date. Many regimens have been tried for the treatment of central fever but there is no therapy has been proved as superior to the others.

Commonly used pharmacological regimens for fever include acetaminophen, acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and corticosteroids [7,11]. Agents such as baclofen and bromocriptine, intravascular cooling devices, and antipyretics have been tried for the treatment of central hyperthermia. Baclofen is a GABA agonist that acts

on the raphe nucleus and inhibits BAT so that core body temperature can be lowered. Side effects of baclofen include drowsiness, fatigue, muscle weakness on the side affected by the stroke or not. The commonly used dose of baclofen is 30-60 mg per day. Bromocriptine is a dopamine D2 agonist that acts on the corpus striatum and hypothalamus. The usual dose is 0.025 mg/kg twice daily which can be increased to 0.05 mg/kg three times daily [2].

Pharmacological management of central hyperthermia is still difficult and antipyretic agents usually do not provide significant benefit. Several medications have been reported to benefit from dysautonomia following traumatic brain injury but their efficacy is less predictable. Such medications include intravenous morphine, midazolam, drugs with sympathetic activity (alpha-adrenergic agonists, some beta-adrenergic blockers), bromocriptine, and intrathecal baclofen [4,12]. Nevertheless, a febrile reaction to intrathecal administration of baclofen was reported in a patient with thoracic syringomyelia [13]. The following are some of the agents that have been reported to be successful in improving central hyperthermia:

#### **Morphine**

Central febrile remission has been reported in patients following traumatic brain injury [14].

#### **Chlorpromazine**

When conventional therapy fails sometimes chlorpromazine is tried and the success rate varies. Chlorpromazine produces antipyretic action due to its ability to improve patients' thermoregulatory lability.

#### **Baclofen**

Baclofen has been reported to be successful in treating long-term central hyperthermia in patients with basilar artery occlusion leading to brainstem infarction [4].

#### **Bromocriptine**

Case studies are reporting the successful use of bromocriptine in central fever [15,16].

#### **Growth hormone therapy**

Successful treatment of central fever with growth hormone therapy has been reported with a mechanism related to the improvement of sweat production [17].

Other methods of lowering the temperature include rotating fans, sponging, and surface cooling devices. However, these methods have limited efficacy and some are uncomfortable for the patient. Surface cooling devices have been reported to in-

crease the incidence of shivering, increase oxygen consumption, and may even cause thermal burns. Hypothermic blankets can trigger large temperature fluctuations. Air blankets are increasing in use and are said to have better efficacy and are more comfortable for patients. Several studies have tried using cold saline intravenous infusion and are said to give promising results without an increase in complications [18]. There have been no large-scale multicenter studies of these devices and methods.

The various neurologic disorders associated with fever require different fever management strategies. Cerebrospinal fluid studies of neurotransmitters, especially GABA and glutamate, can be performed in patients with central hyperthermia. The correlation between neurotransmitter and infarct location may provide better guidance for the management of central fever in stroke [4].

### **THE ROLE OF BACLOFEN IN THE MANAGEMENT OF CENTRAL HYPERTHERMIA**

The use of baclofen that has been approved by the FDA is to treat muscle spasticity, but besides that, baclofen also has several off-label uses. Baclofen (beta-[4-chlorophenyl]-GABA) is a beta subunit agonist of gamma-aminobutyric acid in mono and polysynaptic neurons at the spinal cord and brain levels. Baclofen may be a treatment option in patients with central neurogenic hyperthermia [19]. Baclofen is a GABA agonist that acts on the raphe nucleus and inhibits BAT so that core body temperature can be lowered. The commonly used dose of baclofen is 30-60 mg per day.

Baclofen which is a GABA agonist can function as an inhibitory signal that acts directly on the raphe nucleus in the medulla and successfully stopped hyperthermia in brain stem stroke cases of basilar artery occlusion reported by Huang et al. [4]. This report presents the case of a 68-year-old woman with basilar artery occlusion who experienced long-term hyperthermia. The patient's hyperthermia did not improve with any antipyretic. The patient had also received a water-cooling blanket but her body temperature fluctuates between 35.5 and 40°C. After giving baclofen 30 mg/day the patient's body temperature returned to normal and stable [4].

Lee et al. also reported a case of a patient with a pontine hemorrhage who developed hyperthermia and improved with oral baclofen. Baclofen administration was increased from 30 mg to 60 mg per day. The patient did not experience any specific side effects from the treatment [2].

### **SIDE EFFECTS**

Baclofen has side effects such as drowsiness, fatigue, muscle weakness. These side effects can affect the patient's rehabilitation program. Potential

side effects on several organ systems such as cardiovascular, gastrointestinal, genitourinary, respiratory, neuromuscular, cutaneous, and central nervous systems have been reported. The most common side effects are temporary sedation, confusion, muscle weakness, vertigo, and nausea.

Less common side effects include neuropsychiatric disturbances, hypotension, peripheral edema, dyspnea, hypoventilation, pneumonia, seizures, insomnia, pain, speech alteration, depression, agitation, constipation, diarrhea, urinary frequency, incontinence, acute urinary retention, impotence, tremor, weakness, amblyopia, urticaria, and pruritus. Abrupt discontinuation of oral therapy may cause seizures and hallucinations. Gradual dose reduction is recommended to prevent withdrawal symptoms [19].

## CONTRAINDICATIONS

Baclofen is contraindicated in patients with hypersensitivity to baclofen or any of its components in the formulation. Baclofen should be used with caution in patients with impaired renal function, a dose reduction may be required [20]. Limited data indicate that baclofen has no adverse effects in nursing infants or low levels of the drug in breast milk. However, newborns should be monitored for signs of sedation. The pregnancy category of baclofen is C, baclofen is only given to pregnant women if the benefits outweigh the potential risks to the fetus.

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## MONITORING

Administration of baclofen with other central nervous system depressants requires close supervision. Patients with epilepsy should have periodic EEG monitoring due to deterioration of seizure control while receiving baclofen [19].

## CONCLUSIONS

Central hyperthermia is still a diagnosis of exclusion so that tracing the source of fever must be done thoroughly. There are no guidelines for the management of central hyperthermia to date, but several agents including baclofen have been reported to improve the condition. Baclofen can lower core body temperature with its mechanism of action as a GABA agonist acting on the raphe nucleus and inhibiting brown adipose tissue. The use of baclofen needs to be monitored for side effects that can happen, especially if there is concomitant use of central nervous system depressants. Further studies are still needed regarding the efficacy and safety profile of baclofen as an option for central hyperthermia therapy.

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