

## Long-term potentiation in autonomic ganglia: Potential role in cardiovascular disorders

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### Abstract

Ganglionic long-term potentiation (gLTP) is an activity-dependent, enduring enhancement of ganglionic transmission. This phenomenon may be induced in autonomic ganglia of an organism under certain conditions where

repetitive impulses surge from the central nervous system (CNS) to the periphery. Chronic stress, repetitive epileptic seizure or chronic use of CNS stimulants could induce gLTP, which would result in a long lasting heightening of sympathetic tone to the cardiovascular system causing hypertension and disturbed cardiac rhythm that may lead to sudden cardiac death. These conditions are briefly reviewed in this article.

**Key words:** Electrophysiology; Epilepsy; Ganglionic long-term potentiation; Sudden unexpected death in epilepsy; Central nervous system stimulants; Sudden cardiac death

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**Core tip:** Heightened activity of the central nervous system (CNS) caused by epilepsy, chronic stress and CNS stimulants could provide strong preganglionic stimulation of autonomic ganglia, which may trigger expression of ganglionic long-term potentiation (gLTP). Expression of gLTP can result in cardiovascular dysfunction that may lead to morbidity and even mortality.

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### INTRODUCTION

Before Bliss and Lomo<sup>[1]</sup> coined the term "long-term potentiation (LTP)" in the hippocampus to describe activity-dependent long-lasting potentiation, similar activity-induced enhancement of synaptic transmission was described in the mammalian sympathetic ganglia<sup>[2,3]</sup>. However, it was nearly two decades before ganglionic LTP

**Table 1** Summary of studies reporting ganglionic long-term potentiation of the nicotinic pathway in various animal species

Animal species	Specific ganglia	Ref.
Rat	Superior cervical ganglion	Brown and McAfee <sup>[4]</sup>
		Briggs and McAfee <sup>[6]</sup>
		Alkadhi <i>et al</i> <sup>[15]</sup>
		Alzoubi <i>et al</i> <sup>[25]</sup>
		Alkadhi <i>et al</i> <sup>[28]</sup>
		Alkadhi <i>et al</i> <sup>[29]</sup>
Cat	Superior cervical, lumbar and stellate ganglia	Alkadhi and Alzoubi <sup>[36]</sup>
		Alzoubi <i>et al</i> <sup>[30]</sup>
		Alonso-deFlorida <i>et al</i> <sup>[7]</sup>
Guinea pig	Superior cervical ganglion	Bachoo and Polosa <sup>[8]</sup>
Chick	Parasympathetic ciliary ganglion	Weinreich <i>et al</i> <sup>[9]</sup>
Bullfrog	Sympathetic ganglia	Scott and Bennett <sup>[14]</sup>
		Koyano <i>et al</i> <sup>[11]</sup>
		Kumamoto and Kuba <sup>[13]</sup>
		Minota <i>et al</i> <sup>[10]</sup>

Adapted from Alkadhi K, Alzoubi K. In: Sudden Death in Epilepsy: Forensic and Clinical Issues (Chapter 26). CRC Press, 2011: 395-426.

(gLTP) was characterized in mammalian and amphibian sympathetic ganglia<sup>[4-13]</sup> as well as avian parasympathetic ciliary ganglion<sup>[14]</sup> (Table 1). Later, my laboratory identified serotonin as the neurotransmitter necessary for induction and maintenance of gLTP in the rat superior cervical ganglion<sup>[15]</sup>.

The expression of gLTP is due to a series of events resulting from both the postsynaptic and presynaptic regions, and including activation of enzymes, modulators and second messengers. Whereas LTP of the central nervous system (CNS) is regarded as a cellular mechanism of memory; the function of gLTP is uncertain. It is clear that hyperactivity of the CNS, as in the case of chronic stress or recurrent epileptic seizures, may provide the high frequency stimulation (HFS) necessary to induce the expression of LTP in autonomic ganglia, which may cause deleterious alterations in the cardiovascular system function.

gLTP is induced by repetitive HFS (20 Hz) of pre-ganglionic nerve. Upon cessation of HFS of the pre-ganglionic nerve of rat superior cervical ganglion, test stimuli (0.017 Hz) evoke initial highly potentiated ganglionic responses (compound action potentials), lasting up to 4 min, called post-tetanic potentiation<sup>[15-17]</sup>. This is followed by steady lesser-potentiated action potentials lasting up to 3 h, indicating an increase in synaptic strength<sup>[15,18-20]</sup>.

Published work from this laboratory determined that initiation of gLTP entails both HFS of the preganglionic nerve and stimulation of 5-HT<sub>3</sub> receptors by serotonin originating from certain cells within the superior cervical ganglion of rat<sup>[15]</sup>. Activation of 5-HT<sub>3</sub> receptors is necessary for both initiation and expression of gLTP<sup>[15]</sup>. Extracellular recording revealed that, in ganglia that have

**Table 2** Effects of various 5-HT<sub>3</sub> receptor agonists and antagonists on compound action potential during ganglionic long-term potentiation induced *in vitro* by high frequency repetitive stimulation

Serotonergic drugs	Mode of action	Compound AP
Serotonin (10-20 μmol/L)	Agonist	Increased
Fluoxetine (10 μmol/L)	SSRI	Increased
m-CPBG (1 μmol/L)	Receptor agonist	Increased
Tropisetron (5 μmol/L)	Receptor antagonist	Reduced
Ondansetron (5 μmol/L)	Receptor antagonist	Reduced
MDL 72222 (0.5 μmol/L)	Receptor antagonist	Reduced
Reserpine pretreatment (3 mg/kg)	5-HT <sub>3</sub> depletion	No gLTP
m-CPBG (1 μmol/L) + reserpine	Receptor agonist	Increased

The same drugs produced no significant effect on basal synaptic transmission in control ganglia (adapted from ref. [15,25,29,30,32,33,36]). SSRI: Selective serotonin reuptake inhibitor; AP: Action potential.

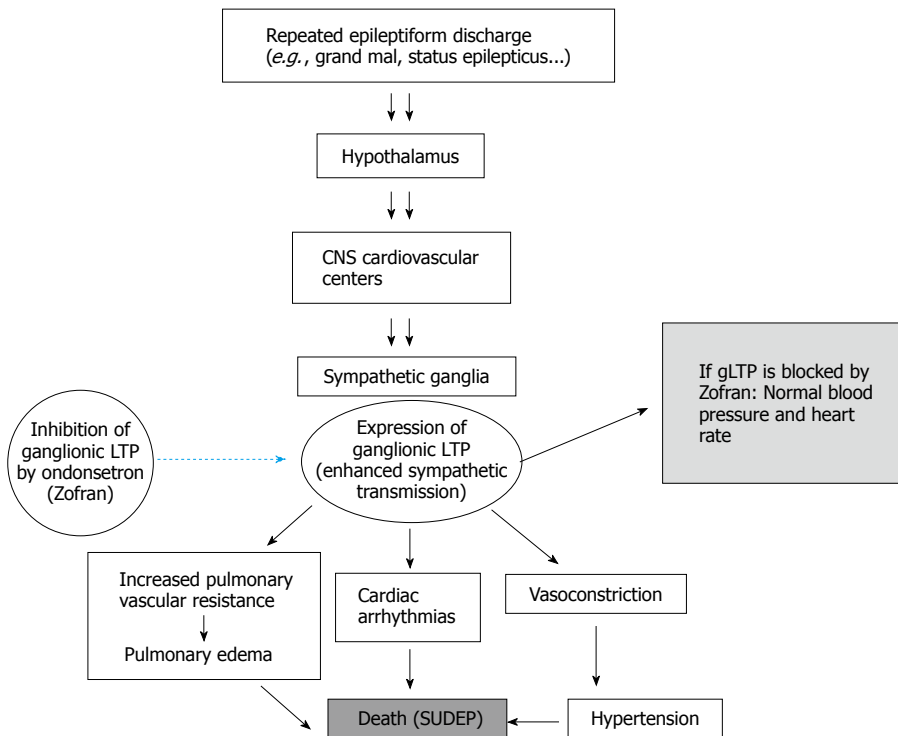
expressed gLTP, serotonin 5-HT<sub>3</sub> receptor agonists and blockers, in concentrations comparable to pharmacological doses in clinical settings, have profound effects on the magnitude of gLTP<sup>[15]</sup> (Table 2), even though the same agents produced no significant effect on basal transmission in ganglia from control rat<sup>[15]</sup>. Thus, we have established gLTP as the first serotonin-dependent LTP ever reported in a mammalian species<sup>[21,22]</sup>.

The 5-HT<sub>3</sub> receptor is a ligand-gated receptor-channel complex, and a member of the superfamily that also includes the nACh receptor<sup>[23]</sup>. It is known that activation of the presynaptic 5-HT<sub>3</sub> receptor causes upsurges in calcium concentration inside rat brain nerve terminals<sup>[24]</sup>. The role of 5-HT<sub>3</sub> receptor in the induction and maintenance of gLTP is presently unclear. Perhaps the activation of 5-HT<sub>3</sub> channel-receptor complex at the nerve terminals in ganglia causes localized entry of calcium ions increasing its intracellular concentration to a level adequate for activation of downstream signaling molecules, including protein kinase C (PKC), calmodulin and calcium-calmodulin kinase II (CaMK II), which are essential for expressing gLTP<sup>[25]</sup>.

## IN VITRO INDUCTION OF GLTP

gLTP can be induced by HFS (20 Hz for 20 s) of the pre-ganglionic sympathetic nerve. This frequency is within the maximum range of *in vivo* firing frequency of preganglionic neurons<sup>[26]</sup>. The response may be measured *in vitro* by intracellular or extracellular recording techniques<sup>[6]</sup>. Furthermore, gLTP has been evoked and recorded *in situ* from ganglia of anesthetized animals<sup>[7,8,27]</sup>.

The LTP of the hippocampal CA1 region and gLTP are similar in various aspects. For example, both are saturable in that when fully expressed, another HFS will not cause additional augmentation of synaptic trans-



**Figure 1** The hypothesis: In the whole animal, epileptic seizures provide the repetitive stimulation required for the expression of ganglionic long-term potentiation in sympathetic ganglia, resulting in increased peripheral resistance, hypertension and cardiopulmonary dysregulation leading to sudden death. Blocking serotonin 5-HT<sub>3</sub> receptor with antagonist (Zofran®) in ganglia has been shown to obviate the effect of gLTP. gLTP: Ganglionic long-term potentiation; CNS: Central nervous system; SUDEP: Sudden unexpected death in epilepsy.

mission<sup>[28]</sup>. Experiments in rat sympathetic ganglia suggest similar molecular mechanisms for the expression of gLTP and hippocampal LTP<sup>[29]</sup>. Both require a ligand-gated ion channel; here is where hippocampal LTP and gLTP differ: Whereas area CA1 hippocampal LTP requires activation of glutamate NMDA receptor, gLTP requires activation of serotonin 5-HT<sub>3</sub> receptor. Similar to NMDA receptor, 5-HT<sub>3</sub> receptor is very permeable to Ca<sup>2+</sup>, which is exceedingly important for launching the molecular cascades responsible for expression of LTP. Strong evidence from this laboratory reveals the involvement of a variety of signaling molecules (e.g., CaMK II, PKC, calmodulin, calcineurin, etc.) in the expression of both hippocampal LTP and gLTP<sup>[30,31]</sup>.

The involvement of endogenous serotonin is indicated by absence of HFS-induced gLTP in ganglia of animals treated with reserpine (3 mg/kg) to remove serotonin. However, when these ganglia were treated with serotonin or m-CPBG (a 5-HT<sub>3</sub>-receptor agonist), HFS invariably induced expression of gLTP (Table 2)<sup>[15]</sup>.

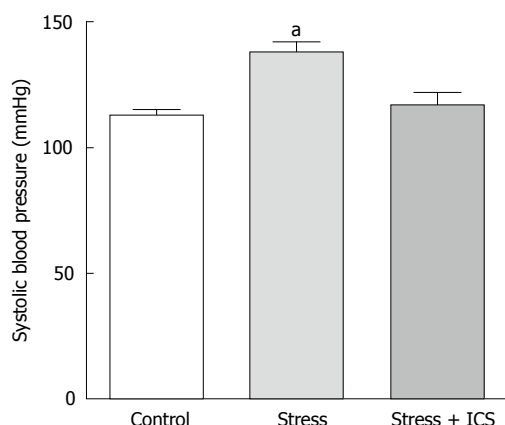
### IN VIVO EXPRESSION OF GLTP

An expected outcome from *in vivo* manifestation of gLTP in ganglia is a long-lasting enhancement of sympathetic tone that outflows to the cardiovascular system. Work from this laboratory has established the consequences of *in vivo* induction of gLTP in sympathetic ganglia on blood pressure<sup>[29,32,33]</sup>. We hypothesize that CNS repetitive activity causes similar outflow to preganglionic nerves, which together with endogenous serotonin may trigger expression of gLTP of sympathetic ganglia. Expression of gLTP produces prolonged and steady increase of

sympathetic tone to the cardiovascular resulting in hypertension and disturbed cardiac rhythm (Figure 1).

We hypothesized that chronic psychosocial stress can induce *in vivo* expression of gLTP in sympathetic ganglia, which results in a constant rise in sympathetic tone thus contributing to or initiating a rise of blood pressure. We tested this hypothesis in four animal models of hypertension; aged rats, spontaneously hypertensive rat (SHR), obese Zucker rat and the psychosocial stress model<sup>[28,33-35]</sup>. We investigated the existence of gLTP in ganglia from these models. For example, in psychosocially stressed hypertensive rats, treatment with tropisetron (ICS; a 5-HT<sub>3</sub> receptor antagonist) resulted in normalizing blood pressure of these rats (Figure 2; ref. [29]). Parallel outcomes were obtained in SHR and obese Zucker rat<sup>[29,32]</sup>. This strongly indicated that the hypertension seen in these animals was, at least partly, due to expression of gLTP.

To further ascertain the existence of gLTP in ganglia isolated from these animal models we showed that "basal" transmission in these ganglia was markedly potentiated (Figure 3A) and that this potentiation was blocked when ganglia were treated with 5-HT<sub>3</sub> receptor antagonists<sup>[29,32,33,35]</sup> (Figure 3B). In another series of experiments, we hypothesized that *in vitro* HFS will not induce gLTP in ganglia isolated from hypertensive old rats if, in fact, gLTP has been expressed already in these ganglia *in vivo*. Whereas HFS produced strong gLTP in ganglia isolated from normotensive adult rats, no gLTP was seen in ganglia from old rats<sup>[28,35]</sup> (Figure 3C). It is worthy to note that in these series, to ascertain the specificity of 5-HT<sub>3</sub> receptor we used three different selective antagonists; bemesetron, tropisetron and ondansetron (Zo-



**Figure 2** Tropicsetron (ICS) normalizes established stress hypertension in psychosocially stressed male rats without affecting blood pressure in control (unstressed) rats measured at day 30 of continuous stress. Blood pressure was measured by tail-cuff plethysmography. Similar results were obtained from female rats. Each point in each group is the mean  $\pm$  SD from 5 male or female rats. (a) indicates significant difference from other groups (Adapted from ref. [29]).

fran), all were equally effective in blocking gLTP<sup>[28,33-35]</sup>.

## POTENTIAL INDUCTION OF GLTP IN BRAIN ILLNESSES AND BY DRUGS

Any procedure that can induce continuous intense flow of impulses from the brain to autonomic ganglia could cause a sustained increase of sympathetic tone to the cardiovascular system, may lead to or contribute to disorders of the system<sup>[28-30,32,33,36]</sup> (Figure 1). The expression of gLTP in autonomic ganglia that may cause hypertension and cardiac arrhythmias can be a serious risk factor for morbidity and mortality. Evidence that associates expression of gLTP with hypertension has been determined for chronic psychosocial stress<sup>[28-30,32,33,36]</sup>. Other possible inducers of gLTP are discussed in the following sections.

## POSTTRAUMATIC STRESS DISORDER

This serious type of stress results from experiencing harsh distressing occurrences for example witnessing injuries or death, exposure to natural disasters, or experiencing a life-threatening accident. Posttraumatic stress disorder (PTSD) is an incapacitating and potentially chronic disorder characterized by substantial illness. Although similar in some features to chronic stress, PTSD has distinctive pathology<sup>[37]</sup>. In the first few years following the traumatic event, some PTSD patients may recover, but up to 40% remain chronically symptomatic for years<sup>[38]</sup>. The major brain areas implicated in the manifestation of PTSD are the prefrontal cortex, amygdala, and hippocampus<sup>[39]</sup>. During a traumatic event the amygdala sends intensifying impulses to various areas of the brain including prefrontal cortex, hypothalamus, hippocampus and brain stem nuclei. During the course of PTSD, intensified brain activity has been described. For example, PTSD patients showed

augmented spontaneous activity in the amygdala and frontal cortex<sup>[40]</sup>. Moreover, PTSD is linked to increased sympathetic activity represented by elevated blood pressure increased heart rate, and/or increased adrenergic transmitter release<sup>[41]</sup>. This increase in sympathetic activity could be due to expression of gLTP in autonomic ganglia. However, whether gLTP is present in ganglia during the progression of PTSD and whether cardiovascular disorders are due to gLTP in autonomic ganglia remain to be explored in animal models of PTSD.

## EPILEPSY

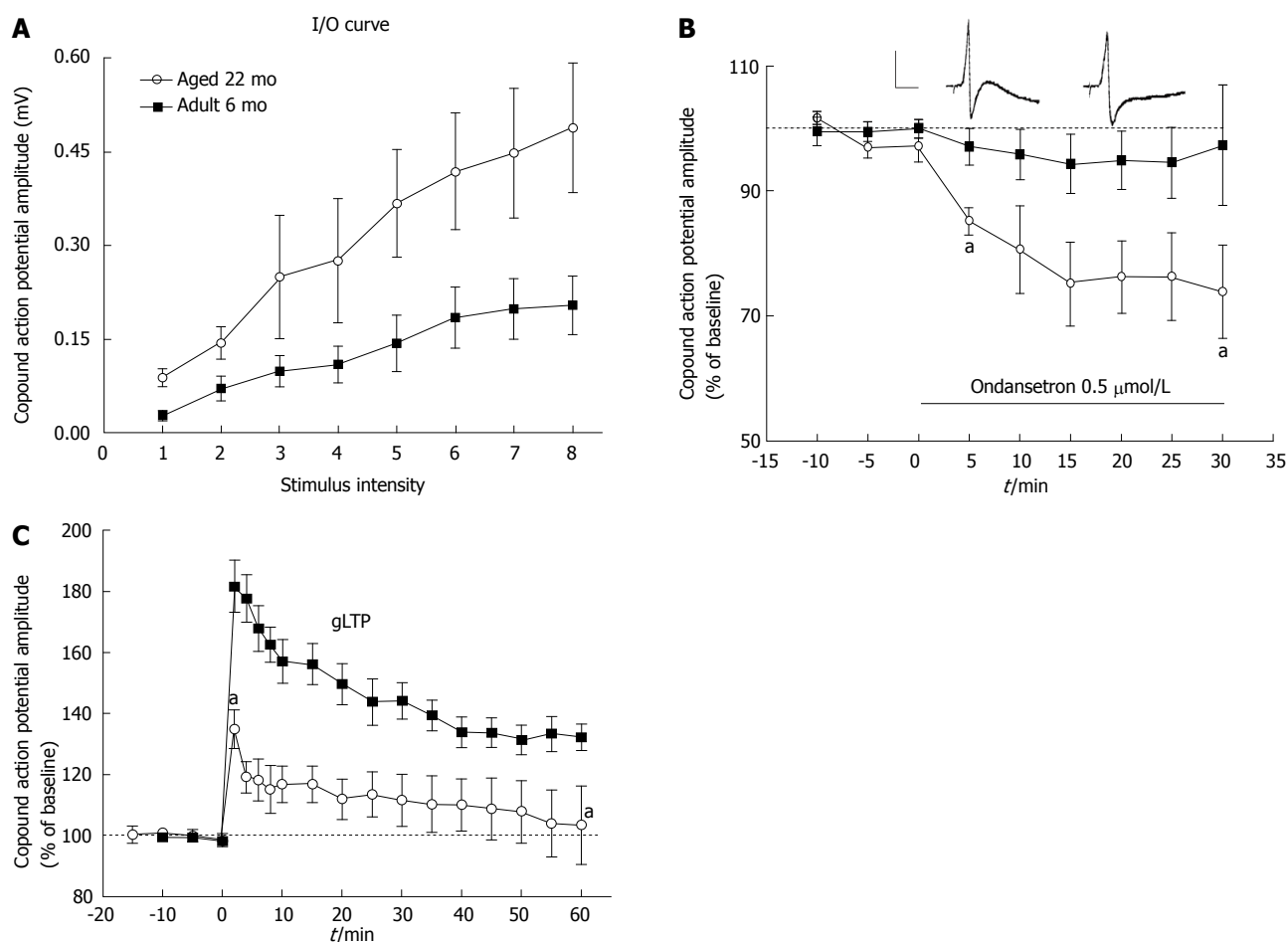
The excessive and abnormal cortical brain activity in epilepsy is transmitted through the brain stem to the rest of the body and can usually cause various types of seizures. Strong stimulation of the sympathetic nervous system often accompany seizures and can cause hypertension, dispersed injury of myocytes, and increased predisposition to ventricular arrhythmias<sup>[42,43]</sup>. Several areas in the brain are involved in the cardiovascular effect of epileptic seizures such as the hypothalamus and medulla oblongata, particularly nuclei of the nucleus tractus solitarius, and area postrema, which are closely engaged in regulation of cardiovascular function<sup>[44-46]</sup>. Therefore, enhanced activity of these areas is communicated to autonomic ganglia and may provide the required repetitive activity that triggers the expression of gLTP in these ganglia. The expression of gLTP results in long-term enhancement of sympathetic tone to the cardiovascular system, causing hypertension and neurogenic cardiac arrhythmias, which can be major risk factors for sudden unexpected death in epilepsy, a dangerous clinical difficulty for certain epileptic patients, especially those with chronic, inadequately controlled seizures.

## NICOTINE

Epileptiform brain activity was recorded in the brains of young rats treated with nicotine<sup>[47]</sup>. In humans, chronic use of tobacco products is known to cause enhanced cholinergic activity in the brain<sup>[48-50]</sup>. Nicotine can also augment peripheral sympathetic activity through activation of postganglionic nicotinic acetylcholine receptors<sup>[51,52]</sup>. Moreover, nicotine can release epinephrine from the adrenal medulla into the blood<sup>[53,54]</sup>. Thus, nicotine causes stimulation of the cardiovascular system that increases heart rate and causes hypertension by action on both peripheral and central sites<sup>[53]</sup>. Hence, since epileptic patients are more likely to be chronic tobacco users<sup>[55]</sup>, such chronic use of nicotine may result in the expression of gLTP in ganglia or enhancement of the impacts of already expressed gLTP in epileptic tobacco users, thus intensify the risk for cardiovascular dysfunction that may cause sudden death<sup>[56]</sup>.

## CAFFEINE

Caffeine, a competitive inhibitor of adenosine receptors,



**Figure 3** Expression of ganglionic long-term potentiation in sympathetic superior cervical ganglia in aged (22 mo) hypertensive rats. A: Input/output curve (I/O) of aged animal ganglia compared to adult (6 mo) ganglia, indicating enhanced synaptic activity in the aged animal ganglia. Stimulus intensity numbers along the X-axis are arbitrary values, where 1 is the minimal and 8 the maximal response (CAP amplitude in mV). Each point from aged rats is significantly different from matching points of adult rats, and is the mean  $\pm$  SEM from 5-7 ganglia; B: Inhibition of "baseline" ganglionic transmission in aged rats by a 5-HT<sub>3</sub> receptor antagonist ondansetron (Zofran) as an indication of expression of gLTP *in vivo*. Zofran (0.5  $\mu$ mol/L, solid horizontal line) decreased CAP baseline of ganglia isolated from aged but not of those isolated from adult rats. All points between the two "a" are significantly different ( $P < 0.05$ ) from corresponding point for adult rats. Each point in each series is the mean  $\pm$  SEM from 5-7 ganglia. Inset: CAPs of aged rats before and after application of drug; calibration 0.5 mV/20 ms; C: High frequency stimulation (HFS: 20 Hz/20 s, at 0 time) of the preganglionic nerves evoked robust gLTP in ganglia excised from adult rats. Identical protocol in ganglia from aged rats produced no gLTP. Each point represents the mean  $\pm$  SEM from 5 ganglia. Adapted from ref. [35]. gLTP: Ganglionic long-term potentiation; CAP: Compound action potential.

is the most extensively used CNS stimulant because it is consumed in a variety of hot and cold drinks, as well as many prescription and over-the-counter medications. Neuroimaging studies reports show that by acting on brain cortex, caffeine enhances attention and mental arousal<sup>[57-59]</sup>. However, there is no convincing evidence that the usual doses of caffeine increase the risk of heart attack, sudden cardiac death, or disruption of cardiac rhythm. Nonetheless, a new caffeine source are the so called "energy drinks", which contain uncommonly hefty doses of caffeine. Consumption of such energy drinks may lead to platelet and endothelial dysfunction, which can cause myocardial infarction and other cardiovascular disorders in healthy young adults<sup>[60-62]</sup> (for review see ref. [63]). Through stimulation of the CNS, heavy frequent intake of caffeine-containing drinks may trigger gLTP in sympathetic ganglia, which could be responsible for the reported cardiovascular disturbances. The danger may be even greater when such consumption of large doses

of caffeine is coupled with heavy use of tobacco products.

## AMPHETAMINES AND COCAINE

The amphetamines work mainly by modifying the catecholamine system in the pleasure center of the brain<sup>[64]</sup>. They increase levels of major catecholamines such as dopamine and norepinephrine in a dose-dependent manner<sup>[65-67]</sup>. A case-control study has linked the use of one of the most commonly used CNS stimulant, methylphenidate (Ritalin), to sudden death in children and teenagers<sup>[68]</sup>.

Cocaine inhibits the monoamine reuptake mechanism in central and peripheral sympathetic nerve terminals in humans<sup>[69-71]</sup> with end effects similar to those seen with amphetamines. This however, may not be the sole CNS effect of cocaine inasmuch as other reuptake inhibitors do not have cocaine-like effects. The abuse of cocaine is correlated with cardiovascular dysfunction including hypertension, ventricular dysrhythmia, acute myocardial



infarction, and left ventricular hypertrophy. Therefore, the chronic use of CNS stimulants such as amphetamine and cocaine may trigger expression of gLTP, which may lead to morbidity and/or sudden death.

## CONCLUSION

Abnormal strong brain activity as in epileptic seizures cause intense activation of ganglionic neurons, which can induce gLTP in sympathetic ganglia leading to long-term heightened sympathetic tone to the cardiovascular system with the ensuing rise in blood pressure and disturbed heart rhythm. Abnormal CNS activity can result from severe brain injuries, ongoing psychological stress, epilepsy, and regular abuse of CNS stimulating substances. Even though these disorders can cause disturbances of the function of the cardiovascular system, their possible link to gLTP has not been studied, except in chronic psychosocial stress. Therefore, it is necessary to determine such links in order to develop therapeutic plans to avoid serious consequences such as sudden cardiac death.

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