

## Acetylcholinesterase and butyrylcholinesterase as markers of low-grade systemic inflammation

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Dear Editor:

Low-grade systemic inflammation plays a significant role in the pathogenesis of insulin resistance, type 2 diabetes mellitus, hypertension, hyperlipidemias, Alzheimer's disease, proliferative diabetic retinopathy; age-related macular degeneration, minimal change nephropathy and various rheumatological conditions.<sup>1,2</sup> Hence, development of reliable, unique and robust markers is essential.

In this context, I noted that plasma and/or tissue levels of acetylcholinesterase and butyrylcholinesterase activities could form reliable indices to detect and diagnose the existence of low-grade systemic inflammation in all the above-mentioned conditions.<sup>3,4</sup> The work of Lampón, *et al.*<sup>5</sup> published in the present issue wherein they observed a significant positive correlation between butyrylcholinesterase (BChE) and hs-CRP though, for hsCRP concentrations > 3 mg/L the correlation between these variables (BChE and hs-CRP) was found to be significantly negative ( $p < 0.001$ ), as in patients with acute inflammation (hsCRP > 10 mg/L) is in support of this contention. It is interesting that BChE activity was negatively correlated with hs-CRP when the latter levels are more than 3 mg/L. The close positive correlation seen between BChE and plasma albumin concentrations not only suggests that hepatic tissue produces these two molecules in a coupled fashion but also implies that when the albumin synthesis is interfered with BChE may not a reliable marker of inflammation.

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### CHOLINESTERASE AND BUTYRYLCHOLINESTERASE

Of the two types of important choline esterases, AChE is a specific esterase that hydrolyzes predominantly choline esters, and characterized by high concentrations in brain, nerve and red blood cells (RBCs). The other type, called BChE, is a nonspecific choline esterase (also called as "pseudo" choline esterase) hydrolyzing other esters as well as choline esters, and found in blood serum, pancreas, liver, and central nervous system.<sup>6,7</sup> The classical action of acetylcholinesterase is to catalyze hydrolysis of acetylcholine within cholinergic synapses of the brain and autonomic nervous system.<sup>8</sup> Although butyrylcholinesterase shares some of these functions, its role in brain remains unclear.

### CHOLINESTERASE AND BUTYRYLCHOLINESTERASE IN DIABETES MELLITUS, HYPERTENSION, INSULIN RESISTANCE, HYPERLIPIDEMIA AND CORONARY HEART DISEASE

AChE was found to be about an order of magnitude higher in islets of Langerhans than in the exocrine tissue in rat pancreas. This difference in activity was found in rats made diabetic with streptozotocin as well as in the controls.<sup>9</sup> The activity of serum BChE was significantly elevated in both type 1 ( $8.10 \pm 3.35$  units/mL) and type 2 ( $7.22 \pm 1.95$  units/mL) diabetes compared with the control subjects ( $4.23 \pm 1.89$  units/mL) ( $P < 0.001$ ).<sup>10</sup> In addition, serum BChE activity correlated with serum fasting triacylglycerol concentration and insulin sensitivity in patients with type 1 and type 2 diabetes. On the other hand, in non-diabetic subjects with BChE deficiency serum triacylglycerol levels were in the normal range, suggesting that BChE might have a role in the altered

lipoprotein metabolism in hypertriglyceridemia associated with insulin insensitivity or insulin deficiency in diabetes mellitus.<sup>10</sup>

Recent studies revealed that plasma (serum), red blood cells and leukocyte activities of enzymes BChE and AChE are elevated in patients with Alzheimer's disease, diabetes mellitus, hypertension, insulin resistance, and hyperlipidemia.<sup>11,12</sup> The observation that BChE activity was inversely related to age and was positively associated with serum concentrations of albumin, cholesterol, and triglycerides, and measures of overweight, obesity, and body fat distribution. In multivariate analysis, the associations of enzyme activity with serum cholesterol, triglycerides, and albumin persisted strongly, and paradoxically individuals in the lowest quintile of BChE activity had significantly higher mortality than those in the highest quintile: all-cause mortality and cardiovascular deaths. The association was attenuated by introduction of serum albumin into the models. These results suggest that low BChE activity may be a nonspecific risk factor for mortality in the elderly.<sup>13</sup> The exact reason for this increased risk of death in those who have reduced activity of the enzyme butyrylcholinesterase is not clear but it indicates that the reduced activity of the enzyme could be as a result of exhaustion of its stores and/or lowered synthesis. Thus, in the initial stages of the diseases: Alzheimer's disease, diabetes mellitus, hypertension, insulin resistance, and hyperlipidemia the activity of the enzyme butyrylcholinesterase is increased whereas in the terminal stages of the disease or when these diseases are advanced and not easily amenable to treatment butyrylcholinesterase activity is low. These results imply that the activity of the enzyme butyrylcholinesterase can be used as a marker to predict the prognosis of these diseases. Hence, it will be interesting to closely monitor those in whom Lampón, *et al.*<sup>5</sup> observed low levels of BChE.

### ACETYLCHOLINE IS AN ANTI-INFLAMMATORY MOLECULE

Acetylcholine (ACh) is the natural agonist for the receptors that also bind nicotine. There are two major types (or classes) of acetylcholine receptors in the body, and they are commonly named by the drugs that bind to them: nicotine and muscarine. Muscarinic acetylcholine receptors (mAChRs) can bind muscarine as well as Ach. Nicotinic AChRs are found throughout the body, but they are most concentrated in the nervous system (the brain, the spinal cord, and the rest of the nerve cells in the body) and on the muscles of the body (in vertebrates). The acetylcholine receptor modulates

interactions between the nervous system and the immune system.

The nervous system communicates with the immune system in a bi-directional pathway. Nervous tissues synthesize neuropeptides and cytokines that communicate with immune cells and serve as the molecular basis of neural-immune interactions. The cholinergic anti-inflammatory pathway signals through the efferent vagus nerve and is mediated primarily by nicotinic acetylcholine receptors on tissue macrophages: the pathway leads to decreased NF- $\kappa$ B activation, preservation of HMGB1 nuclear localization and decreased production of proinflammatory cytokines. There is evidence that activation of afferent vagus nerve fibers by endotoxin or proinflammatory cytokines stimulates hypothalamic-pituitary-adrenal anti-inflammatory responses that lead to anti-inflammatory signals through the efferent vagus nerve, which has been termed the cholinergic anti-inflammatory pathway.<sup>14</sup> This anti-inflammatory pathway is mediated primarily through nicotinic acetylcholine receptors that are expressed on macrophages. Acetylcholine reduced nuclear factor (NF- $\kappa$ B) activation, preserved high mobility group box 1 protein (HMGB1) to its nuclear localization and reduced production of inflammatory cytokines. Modulation of this axis through direct electrical stimulation of the peripheral vagus nerve during lethal endotoxemia in rats inhibits tumor necrosis factor- $\alpha$  synthesis in the liver, attenuates serum TNF- $\alpha$  level, and prevents the development of shock.<sup>15</sup> *In vitro* studies revealed that nicotine is associated with a reduction in activation of the proinflammatory transcriptional factor NF- $\kappa$ B in macrophages, an effect that is mediated by the specific nicotinic acetylcholine receptor,  $\alpha$ 7nAChR.<sup>16</sup>

The efficacy of nicotine may also be explained in part by an inhibitory effect on release of HMGB1, a potentially important late mediator of lethal sepsis.<sup>17</sup> Since acetylcholine is anti-inflammatory in nature, it reinforces the importance of this "cholinergic anti-inflammatory pathway" in the inflammatory process and its resolution.

### ACETYLCHOLINESTERASE AND BUTYRYLCHOLINESTERASE SERVE AS MARKERS OF INFLAMMATION

Since acetylcholine is an anti-inflammatory molecule, when the concentrations of enzymes AChE and BChE are increased it will lead to reduced levels of acetylcholine. This leads to absence or a reduction in the anti-inflammatory actions exerted by acetylcholine. Thus, increased plasma, CSF, leukocyte, RBC, platelet,

and other tissue concentrations of AChE and BChE enzymes indirectly reflect reduced concentrations of acetylcholine and so increase in the local and systemic inflammation. Hence, it is reasonable to propose that activities of AChE and BChE are increased in all the inflammatory conditions even when plasma and CSF and tissue concentrations of CRP, IL-6, TNF- $\alpha$  and other markers of inflammation are not appreciably elevated. Thus, increase in the activities of enzymes AChE and BChE in the plasma, CSF, RBC, leukocytes (including macrophages and T cells), platelets, and other tissues form a reliable, unique and specific marker to detect acute, chronic and low-grade systemic inflammation.

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