# Circulating Serotonin, Catecholamines, and Central Nervous System Circuitry Related to Some Cardiorespiratory, Vascular, and Hematological Disorders

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## ABSTRACT

This review presents results that show that assessment of circulating neurotransmitters is the most effective and, indeed imperative, way to attain a scientific approach to the autonomic nervous system (ANS). The resulting ANS profile makes it possible to prescribe neuropharmacologic therapies to correct central nervous system circuitry disorders responsible for the abnormalities registered at the peripheral ANS level. Some examples of disastrous therapeutic trials based on poor knowledge of neuropharmacology and the ANS in general are provided. In addition, data regarding the protagonist role exerted by circulating plasma serotonin in pulmonary bronchoconstriction, pulmonary vasoconstriction, and platelet serotonin in both cardiovascular and hematological disorders are given. All of these disorders were dramatically improved by the administration of neuropharmacologic agents that affected both platelet and neuronal serotonin uptake.

## INTRODUCTION

A great deal of published research presents results dealing with the assessment of the autonomic nervous system (ANS). Physiologic, pharmacologic, and clinical parameters have been tested in order to reach a reliable approach to that target. Cardiovascular and/or circu-

lating catecholamines are the most frequently assessed parameters used to evaluate the "so called" peripheral ANS. This over-simplified concept underlies the "two-faces coin" paradigm: sympathetic versus parasympathetic activity. This peripheral neuroautonomic profile does not take into account that the central nervous system (CNS) circuitry, which includes noradrenergic, adrenergic, dopaminergic, serotonergic, and acetylcholinergic neuronal nuclei, displays physiologic interactions that redound in peripheral ANS activity. Hence, the assessment of ANS activity should be carried out on the basis of the measurement of all, and not some, circulating neurotransmitters released from glandular plus neural sources.

In addition to the above, these parameters should be measured during basal as well as after the application of different physiologic stimuli. The rationality of these testing procedures is based on the well-known fact that neural sympathetic, adrenal sympathetic, and parasympathetic branches respond differently to specific stimuli under both physiologic and pathophysiologic situations.[1-7]

This review summarizes the results obtained from the assessment of circulating neurotransmitters as well as other physiologic parameters in 30,000 normal and diseased persons throughout the past 25 years.[8-23] In addition, the effects of many neuropharmacologic drugs whose CNS and peripheral-acting mechanisms that have been well established are also examined. These procedures assessed the particular contribution of the neural sympathetic, adrenal sympathetic, and parasympathetic systems to the peripheral neuroautonomic profile of the subjects investigated. In addition, the neurophysiologic and neuropharmacologic mechanisms that shed some light on the CNS-peripheral autonomic crosstalk are discussed.

## CIRCULATING SEROTONIN

Circulating serotonin (5-hydroxytryptamine or 5-HT) arises from the enterochromaffin cells. Parasympathetic drive plus hormonal- plus food-derived chemicals trigger 5-HT release to both intestinal lumen and portal circulation.[24,25] In addition, circulating catecholamines are also able to activate enterochromaffin cells.[26] The fraction of intestinal 5-HT released to the peripheral circulation is cleared by the liver and lungs.[27] Finally, all 5-HT that escapes from the liver plus lungs clearance is taken up and stored by platelets (p-5-HT).[28] However, a very small fraction of circulating 5-HT remains free in the plasma (f-5-HT).

f-5-HT is rapidly taken up by the lungs (in vitro perfusion systems), which are able to clear 70% to 90% of exogenously infused 5-HT during one passage through the pulmonary circulation.[29] An intact endothelium, particularly in the microvasculature, seems to be a prerequisite for normal clearance of 5-HT, and 5-HT is metabolized within these cells.[30] In human airways, 5-HT is localized at nerve endings in the pulmonary neuroendocrine cells (PNEC)[31] and may be released upon exposure to local airway conditions such as hypoxia, hyperoxia, and hypercapnia.[32,33] PNEC are granulated epithelial cells and can be detected throughout the lung from the trachea to the alveoli.[34] PNEC constitute the vagal presynaptic element and the vagal nerve endings, the postsynaptic element.[35]

Total circulating serotonin (5-HT) includes platelet-serotonin (p-5-HT; normal values (NV) = 150-250 ng/mL) plus free-serotonin in the plasma (f-5-HT; NV= 0.7-1.5 ng/mL). Both p-5-HT and f-5-HT increase during postprandial periods[8] and other hyperparasympathetic (physiologic or pathophysiologic) situations.[36-38] Increased release from enterochromaffin cells accounts for the

p-5-HT rise,[37-39] whereas increased levels of circulating acetylcholine (ACh) that interfere with platelet uptake of 5-HT are responsible for augmented f-5-HT plasma levels.[1,2] Conversely, increased circulating catecholamines are responsible for the lowered p-5-HT and the increased f-5-HT registered during stressful situations that trigger platelet aggregation.[2,38]

## CIRCULATING CATECHOLAMINES

Two different pools constitute circulating catecholamines: adrenal gland secretions and neural sympathetic release. Adrenal gland catecholamines consist of adrenaline (Ad) (75% to 80%), plus noradrenaline (NA) and dopamine (DA), which account for the remaining 20% to 25%. However, some fraction of circulating catecholamines can be taken up by sympathetic terminals, to be further released together with the NA plus DA synthesized in these terminals.[40] Neural sympathetic release of catecholamines comprises 80% to 90% NA plus 10% to 20% DA. Both NA and DA are synthesized in separate pools. The latter is released before the former and exerts a modulatory role by acting on $DA_2$ receptors existing at sympathetic terminals.[41-43]

## CNS CIRCUITRY RESPONSIBLE FOR SEROTONERGIC PLUS CATECHOLAMINERGIC ACTIVITIES

Although circulating 5-HT does not cross the blood brain barrier, a close and complex anatomic plus physiologic crosstalk takes place between central and peripheral 5-HT activities, as well as among serotonergic plus catecholaminergic and parasympathetic activities. However, this review refers only to some well-established findings considered basic to a general understanding by readers.

The CNS–5-HT system includes six neuronal nuclei located at the midline throughout the pontine-midbrain and medullary regions: the dorsal raphe (DR), median raphe (MR), periaqueductal gray (PAG), raphe magnus (RM), raphe obscurus (RO), and raphe pallidus (RP).[44,45] These serotonergic nuclei display direct and indirect modulation on all sympathetic and parasympathetic (medullary, hypothalamic, and spinal) nuclei.[46] This is possible due to complex polysynaptic mechanisms that modulate the peripheral ANS and depend on a broad web of direct and indirectly driven information (crosstalk). For instance, the nucleus RO sends direct excitatory axons to the medullary motor vagal complex (dorsal motor + nucleus ambiguus).[47-50] In turn, the 5-HT-RO receives excitatory sensory vagal nuclei (dorsal + area postrema).[51] The area postrema is located outside the blood brain barrier and thus is accessible to the blood stream. This nucleus is crowded with $5\text{-HT}_3$ receptors that can be excited by plasma 5-HT.[52] According to this, any f-5-HT increase in the plasma triggers parasympathetic activation, which in turn, will increase ACh plasma levels.[53,54] Considering that plasma ACh interferes with 5-HT uptake by platelets, any f-5-HT increase in the plasma will trigger further excitation of the area postrema. This excitatory drive is transmitted to the motor vagal complex and vagal nerves, whose discharge at intestinal enterochromaffin cells triggers 5-HT release. This parasympathetic positive feedback will result in a further increase of circulating ACh, which in turn, will boost f-5-HT plasma levels.[53,54] This positive serotonergic-parasympathetic feedback constitutes the called Bezold-Jarisch reflex, responsible for uncontrollable symptoms such as nausea, vomiting, diarrhea, blood pressure decrease, etc.

Other examples of the central-peripheral crosstalk may be seen. For instance, PAG and MR serotonergic

nuclei send excitatory and inhibitory axons, respectively, to the C1-Ad (adrenaline neurons) located at the rostral ventrolateral medullary areas.[55-59] These C1-Ad nuclei are directly responsible for adrenal gland secretion as shown by retrovirus tracing.[60] Conversely, a RP serotonergic nucleus sends excitatory axons to spinal sympathetic preganglionic neurons located at the intermediolateral columns of the thoracic plus lumbar sympathetic segments. These preganglionic (ACh) sympathetic neurons send ACh-preganglionic axons to the postganglionic (NA) cells, located at the sympathetic ganglia, whose axons constitute the sympathetic nerves.[61,62] Thus, peripheral sympathetic activity is made up of two separate systems, ruled by two different CNS circuits.

In short, the sympathetic preganglionic neurons that send axons to adrenal glands are directly ruled by C1-Ad medullary nuclei, while the sympathetic preganglionic neurons sending axons to sympathetic ganglia belong to a separate circuit and receive direct axons from the NA(A5) plus NA(A6) pontine nucleus.[63] However, both central preganglionic sympathetic neurons receive serotonergic modulatory axons. According to the above, two different branches of peripheral sympathetic activities exist, and these two branches converge to form the pool of plasma catecholamines.[64-69] One part of that pool arises from NA-DA released from sympathetic nerves, while the other pool (Ad + DA + NA) arises from adrenal gland secretion.[65-71]

## PULMONARY VASOCONSTRICTION

Pulmonary vasoconstriction is the main pathophysiologic disorder in both primary and secondary pulmonary hypertension. It is characterized by raised pulmonary vascular resistance, which results in diminished right-heart function due to increased right ventricular afterload. Pathogenic mechanisms that deal with this syndrome focus on abnormalities in the interaction between endothelial and smooth muscle cells that require mediators favoring vasoconstriction. Pulmonary artery branches are compliant structures with few muscle fibers, allowing the pulmonary vascular bed to function as a high-flow, low-pressure circuit. Many circulating vasoactive mediators have been postulated to play a part in pulmonary hypertension, including 5-HT,[72-76] which has been found raised during acute periods. With respect to this, plasma catecholamines and indolamines (5-HT) in 11 primary pulmonary hypertension cases plus two cases associated with scleroderma and three associated with Raynaud disease have been investigated. In addition, 16 patients with secondary pulmonary hypertension (two with vasculitis, three with chronic bronchitis, nine with chronic bronchial asthma, and two with obesity) have been examined. All of these patients were investigated during relapse as well as relief periods. Although the supine resting plus orthostasis plus exercise test was performed during the latter period, only supine-resting assessment was performed during relapse.[77-81]

The results showed that although all patients with pulmonary hypertension showed raised f-5-HT plasma values during relapses, opposite profiles were registered during relief periods. Patients who presented with scleroderma and Raynaud disease had very high NA/Ad plasma ratio and very low plasma tryptophane levels. Conversely, the other patients (those with vasculitis, chronic bronchitis, obesity, and bronchial asthma) with pulmonary hypertension but not scleroderma or Raynaud disease showed low NA/Ad ratio (<2) and normal tryptophane plasma levels. These opposing plasma neurotransmitter profiles showed an absolute neurosympathetic over adrenal sympathetic

predominance in the former whereas the opposite profile is seen in the latter group. These two plasma catecholamine profiles are similar to those found in patients with essential and nonessential hypertension, respectively.[9,10,71]

The fact that a small dose of oral tianeptine (12.5 mg), a drug that enhances 5-HT uptake, suppressed acute symptoms in patients with pulmonary hypertension within the first hour of its administration showed that the f-5-HT plasma peak was responsible for worsening the symptoms. It is logical to assume that the abrupt f-5-HT rise registered in secondary pulmonary hypertension is triggered by increased platelet aggregability, secondary to increased plasma levels of Ad that were registered in these patients. However, this factor is absent in patients with primary pulmonary hypertension. The fact that these patients showed greatly raised plasma levels of DA during pulmonary hypertension relapses should be noted, in accordance with the incontrovertible fact that not only ACh, but also DA, interferes with platelet serotonin uptake.[82,83] Obviously, the circulating DA rise that registered in patients with primary pulmonary hypertension during attacks came from the DA pool existing at sympathetic terminals, which is not only co-secreted with NA but is released before NA during neural sympathetic discharge.[42,43] For instance, it is known that NA(A6) plus NA(A5), DR-5-HT, and MR-5-HT pontine neuronal nuclei show progressive reduction of their "firing activity" throughout the four slow wave sleep (SWS) stages and, further, they show zero firing activity during REM sleep.[84,85] This slope is paralleled by the NA but not the Ad plasma slope.[11,86,87] NA plasma levels fall progressively and reach minimal levels at the REM sleep stage whereas Ad plasma levels fall abruptly during the first 10 minutes of supine resting position, when the subjects are still awake. These findings are consistent with the observation that the NA pontine activity fades progressively throughout sleep periods. Patients affected by essential hypertension showed no NA plasma fall during sleep and, moreover, presented no REM sleep stage, which is consistent with the hypernoradrenergic activity found in this type of hypertensive patient.[9-11,71,86,87]

The investigation of circulating neurotransmitters throughout wake-sleep periods in patients showing the "uncoping" stress profile revealed that they had a very low NA/Ad plasma ratio during wake and sleep stages alike. The NA plasma level fell abruptly during the supine-resting period. They did not present the normal SWS fading and abruptly reached the REM sleep stage.[12-16,88,89] This is explained by the exhaustion of NA pontine neurons registered in "uncoping" stressed mammals.[88] Plasma catecholamine values are greater than normal during REM sleep stage in "uncoping" stressed mammals; however, the NA/Ad ratio shows minimal values at this period because of the absolute absence of neural sympathetic activity. It is consistent with the knowledge that nocturnal cardiovascular, cerebrovascular, and respiratory attacks usually occur at REM periods in stressed subjects who show maximal C1-Ad over the NA pontine neurons predominance at this sleep stage.

The f-5-HT/p-5-HT plasma ratio registered during REM sleep is an appropriate parameter of the parasympathetic activity when tested in normal subjects. This f-5-HT/p-5-HT ratio profile is paralleled by the low blood pressure and minimal pulse rate registered in normal subjects. These findings are consistent with the fact that both NA and Ad reach minimal levels at this period.[11]

ACh interferes with platelet uptake, which is consistent with the raised f-5-HT/p-5-HT ratio found during the REM

sleep period, at which time maximal parasympathetic activity is registered. This peripheral parasympathetic hyperactivity would be positively associated with findings showing that the midbrain and medullary ACh neurons display maximal activity during the REM period. However, the raised f-5-HT plasma levels registered throughout the abnormal sleep stages in "uncoping" stressed subjects do not reflect parasympathetic activity but platelet aggregation, secondary to the high Ad plasma levels they always present. These findings should be viewed as examples of the CNS-peripheral autonomic crosstalk.

An additional concern is expressed here regarding the identification of CNS-autonomic disorders triggered by the consumption of sleeping pills and antidepressants that provoke a distortion of the wake-sleep cycle and, consequently, trigger physiologic disorders in both CNS and peripheral autonomic systems.[90-93]

## ARTERIAL HYPERTENSION

Two types of hypertensive subjects, according to their plasma neurotransmitter profiles were found: patients with essential hypertension and those with nonessential hypertension. The former group showed a greater than normal NA/Ad plasma ratio and low tryptophane plasma levels, whereas the latter showed a low NA/Ad ratio (<2) and normal or raised tryptophane plasma levels. f-5-HT and plasma DA were normal in the former group, while f-5-HT and plasma Ad were elevated in the second group. A close positive correlation was found between DA versus f-5-HT in patients with essential hypertension, whereas a close positive correlation was also found between Ad versus f-5-HT in the nonessential hypertension group.[9,10,71] Because DA interferes with p-5-HT uptake[42,43,94] and Ad triggers platelet aggregation, this agrees with the above-mentioned correlations, respectively.[3]

Because the rat model of essential hypertension presents increased activity of NA pontine neurons[95-100] and the rat model of "uncoping" stress situation is characterized by exhausted NA pontine neurons plus hyperactive C1-Ad nuclei,[4,101] these two hypertensive profiles might be extrapolated to humans.[9,10,71,100,101]

## CHRONIC CONGESTIVE HEART FAILURE

Although patients with chronic congestive heart failure (CCHF) show raised catecholamine circulating levels, their plasma NA/Ad ratio is very low, revealing absent NA pontine activity. The failure by Swedberg et al,[102] who attempted to treat these patients with an imidazoline agonist on the grounds that patients with CCHF presented "so called" hypersympathetic activity, occurred because the investigators ignored that the two peripheral sympathetic activities do not constitute a unit, but rather two well-differentiated sympathetic systems that display associated or dissociated activities.[69,71,103-106]

The appropriate parameter for assessing the two branches of the sympathetic system should be based on the assay of plasma catecholamines in order to find the NA/Ad ratio, and not the sum of NA and Ad. This assessment should be carried out throughout the complete supine resting plus 1-minute orthostasis plus 5-minute moderate exercise test.[5,69,107] This test has been performed in 30,000 healthy and diseased persons throughout the last 20 years.[97] The normal value of NA/Ad ratio at 1-minute orthostasis was found to be 3 to 4. The diastolic blood pressure, but not the systolic blood pressure, should peak in normal subjects at orthostasis. This diastolic blood pressure peak parallels NA plasma rise and directly depends on the NA pontine neuronal firing, which

activates lumbar sympathetic preganglionic neurons and is transmitted to sympathetic nerves.[108,109] The 1-minute orthostasis test reflects the normal dissociation between the two branches of sympathetic activities.[5,40,69,99,106,109-113] This NA/Ad ratio increases in patients who show NA pontine over C1-Ad predominance, such as neurogenic hypertension,[9,10,98,99] Raynaud disease,[114] scleroderma,[114] endogenous depression,[17,18] primary pulmonary hypertension,[76,115] and most autoimmune diseases that are labeled as presenting with a TH-1 immunological profile.[116] Conversely, the low NA/Ad plasma ratio is registered in diseases presenting an "uncoping" stress neurochemical profile, eg, bronchial asthma, secondary pulmonary hypertension, gastroduodenal ulcer, most types of cancer and infectious diseases, and autoimmune diseases that show a TH-2 cytokine profile.[6,116,117]

The two types of sympathetic preganglionic neurons are modulated by serotonergic axons, and this is a clear example of serotonergic sympathetic crosstalk. This phenomenon is evident during sleep, during which different stages are paralleled by NA, Ad, f-5-HT, p-5-HT, and tryptophane blood changes. Considering that the neurophysiologic changes of the different NA, Ad, 5-HT, and ACh CNS nuclei that occur throughout the four slow-wave and REM sleep periods are well known, it is possible to investigate the parallels between CNS and circulating neurotransmitters changes.[6,117-121]

These findings are consistent with the postulated pathogenic role assigned to f-5-HT as the trigger of pulmonary hypertension relapses. These comments are also consistent with the worsening of all types of pulmonary hypertension when treated with drugs that augment f-5-HT plasma levels, like fenfluramine, sertraline, paroxetine, fluoxetine, and other 5-HT uptake-inhibitors.[122-124] Conversely, the dramatic suppression of pulmonary hypertension symptoms induced by tianeptine, a drug that enhances platelet uptake and triggers an abrupt disappearance of f-5-HT from the plasma, gives additional support.[46,77-79,81]

## CIRCULATING 5-HT AND BRONCHOCONSTRICTION

Studies have shown that levels of f-5-HT in plasma are elevated in symptomatic asthmatic patients during attacks.[15,118-122] In addition, the plasma concentration of f-5-HT in symptomatic patients with asthma correlates positively with clinical status and negatively with pulmonary function ($FEV_1$).[125-129] 5-HT facilitates cholinergic contractions in human airways in vitro through stimulation of both prejunctional $5\text{-}HT_3$ and $5\text{-}HT_4$ receptors.[130-135]

Although symptomatic patients with asthma have increased plasma levels of NA, Ad, DA, f-5-HT, and cortisol when compared with asymptomatic patients with asthma, f-5-HT was the only factor closely associated with clinical severity and pulmonary malfunction. Other data show that f-5-HT is actively transported by the pulmonary endothelial cells, where it is metabolized by the monoamine oxidase enzyme.[132] In addition, 5-HT causes constriction of both central and peripheral airways when given to vagotomized cats and other mammals. Further data show that inhaled 5-HT induces an acute fall in lung function (>20% in $FEV_1$) in asthmatic patients but not in normal subjects.[133135]

Potential sources of 5-HT within the pulmonary system include platelets and nerve terminal (PNEC) cells. In humans, 5-HT is concentrated in platelets and is released when platelets aggregate. Platelet aggregation occurs during stressful situations and is common in immunological diseases.[136-139]

Bronchoconstriction evoked by f-5-

HT involves vagal afferent nerves, and it is inhibited by atropine. f-5-HT can induce bronchoconstriction by affecting presynaptic neuronal 5-$HT_3$ receptors at the medullary area postrema, located outside the blood brain barrier.[140-149] Increased parasympathetic activity is associated with asthma attacks. Parasympathetic activity releases 5-HT at the intestinal level and provokes an increase of blood 5-HT. In addition, hyperparasympathetic activity (as occurs during sleep and postprandial periods) interferes with p-5-HT uptake, which enhances f-5-HT in the plasma, thereby triggering asthma attacks. Buspirone, a drug that increases central and peripheral parasympathetic activity, provokes asthma attacks in patients with asthma.[19] Tianeptine, a drug that enhances 5-HT uptake by platelets and reduces f-5-HT in the plasma, suppresses asthma attacks within the first hour after administration.[20,21] It is difficult to know if the dramatic suppression of asthma attacks induced by tianeptine should be attributed to peripheral and/or central effects. This drug enhances the uptake of 5-HT by serotonergic terminals. These 5-HT axons release 5-HT at the medullary respiratory center responsible for the activation of this function.[150-152]

## CIRCULATING 5-HT AND PLATELET DISORDERS

### Refractory Idiopathic Thrombocytopenic Purpura

Refractory idiopathic thrombocytopenic purpura (ITP) is a severe pathophysiologic disorder characterized by the development of autoantibodies that destroy platelets. It is included among the TH-2 autoimmune diseases in accordance with the cytokine profiles registered in the blood of these patients.[153-157] Patients with ITP who do not improve with immunosuppressant therapy are considered refractory, and they usually undergo splenectomy. Nevertheless, an important percentage of splenectomized patients with ITP show severe and uncontrollable relapses. The assessment of circulating catecholamines and indolamines performed at the Institute of Experimental Medicine**,** Universidad Central de Venezuela, on those refractory patients with ITP revealed that there was no correlation between the number of platelets and the amount of p-5-HT. In addition, the bleeding disorders correlated negatively with the p-5-HT values rather than with the platelet count.[157-160] Finally, all of these patients showed increased levels of f-5-HT as well as very high levels of plasma Ad, which was responsible for their very low NA/Ad plasma ratio. Because the administration of tianeptine, a drug that enhances 5-HT uptake by platelets, triggered a dramatic disappearance of bleeding episodes, this supports the hypothesis that 5-HT plays a primordial role in platelet activation. However, a definite improvement of patients with ITP was achieved by the normalization of the NA/Ad ratio with neuropharmacologic therapy.[157]

### Polycythemia Vera

Polycythemia vera (PV) is a myeloproliferative disorder of unknown cause. PV is associated with a NA over 5-HT predominance that is paralleled by a TH-1 over TH-2 immune profile;[116] this lead the investigators to prescribe neuropharmacologic therapy to reverse this neuroautonomic unbalance.[161] Normalization of the neurochemical CNS disorder triggered by neuropharmacologic therapy was followed by restoration of both the normal ANS profile and the immunological peripheral balance.

It is important to emphasize the role played by p-5-HT as a thrombogenic factor. It has been shown that the platelet content of 5-HT rather than the platelet count itself is the most important factor involved in hemosta-

sis.[157,162,163] The disappearance of thrombotic episodes in a patient with PV occurred 3 weeks after start of neuropharmacologic therapy, at which time p-5-HT, but not the platelet count, dropped.[116,161] This finding is the mirror image of that observed in purpura thrombocytopenic patients, in whom the bleeding stoppage was paralleled by the p-5-HT increase rather than the platelet number increase.[157,162-164] This phenomenon was discussed in several papers, and it assigned a fundamental role to p-5-HT in all types of thrombotic events, which can be eliminated by lowering platelet 5-HT content with drugs that interfere with 5-HT uptake by both platelets and serotonergic neurons.[158-160,165] Finally, reversion of the TH-1 immunologic profile seen in patients with PV following reversion of the CNS-NA over 5-HT predominance suggests that this immunologic disorder underlies the etiopathogenesis of this disease.

The spleen bone marrow and all hematopoietic organs receive neural sympathetic innervation. Sympathetic nerves arise from the lumbar spinal sympathetic neurons that send preganglionic axons to sympathetic ganglia. Such preganglionic branches contact postganglionic sympathetic neurons (located at this level), which innervate the aforementioned hematopoietic organs. In turn, spinal sympathetic preganglionic neurons receive axons from the NA pontine nuclei, which is the main center responsible for neural sympathetic activity. These facts explain the beneficial therapeutic effects exerted by CNS-acting drugs that potentiate serotonergic neurons that bridle NA pontine nuclei in improving patients with PV.

**Carcinoid Syndrome**

Carcinoid syndrome is another example of adrenal over neural sympathetic predominance plus raised levels of circulating p-5-HT and f-5-HT, as well as a TH-2 immunological profile. These patients were treated with neuropharmacologic therapy to revert the neuroimmunologic profiles.[166,167] Both neuroautonomic and immunologic disorders should be included among the pathophysiologic mechanisms underlying this disease (TH-2 profile). This inference is reinforced by all clinical, ANS, and immunologic improvements that were triggered by neuropharmacologic manipulations similar to those used to revert Ad over NA predominance.

The raised circulating 5-HT level found in carcinoid patients agrees with the enterochromaffin cell overactivity that is always present in this disease. Furthermore, because p-5-HT remained elevated whereas the f-5-HT was normalized in these patients after clinical improvement, and although their enterochromaffin cells remained overactive, the symptoms appear to have been related to the raised f-5-HT plasma levels. Both the physiologic disorders and their clinical symptoms were paralleled by adrenal over neural sympathetic predominance periods. This phenomenon may be associated with the maximal ability of the neural sympathetic system to annul the parasympathetic drive, which is responsible for enterochromaffin cell secretion and for increased f-5-HT levels, all of which occurs during excessive parasympathetic drive. The increase of f-5-HT registered in these circumstances may be exacerbated because this indolamine excites $5\text{-HT}_3$ and $5\text{-HT}_4$ receptors located at the medullary area postrema (outside the blood brain barrier), which is connected to the motor vagal complex.[100] This results in further increase of the peripheral parasympathetic drive discharge over the enterochromaffin cells (Bezold-Jarisch reflex). Such mechanisms may explain the hyperserotonergic storm that occurs in carcinoid patients.

The enhancement of natural killer

cells (NK-cell) cytotoxicity as well as the shifting of TH-2 to TH-1 immunologic profile, triggered by the neuropharmacologic therapy prescribed to these carcinoid patients, merits special mention. In 1987, neuropharmacologic therapy was able to improve patients with different types of cancer.[22] In addition, the clinical improvement was paralleled by an increase in NK cell activity.[40,45,168,169] These reports were further confirmed in other studies.[16,170-171] It was also shown that clinical severity in patients with cancer correlated negatively with NA/Ad ratio, whereas clinical improvement showed positive correlation with NA/Ad. The forgoing findings are in line with those by other investigators who showed that some drugs which improved colon and lung cancer triggered NK cell activation.[170]

## CONCLUSION

Extensive experimental, clinical, and therapeutic data have been presented that show that the assessment of all (but not one or two) circulating neurotransmitters is the only effective way to accurately evaluate the peripheral ANS. Furthermore, a reliable evaluation depends on assessing neurotransmitters not only during basal (supine-resting) but also at orthostasis and exercise stress periods. Data demonstrating successful therapeutical approaches to bronchial asthma, pulmonary vasoconstriction, carcinoid syndrome, and platelet disorders were presented. In addition, data dealing with the peripheral and CNS autonomic disorders that underlie the pathophysiology of CCHF and arterial hypertension were shown. Furthermore, broad scientific data dealing with the CNS circuitry responsible for controlling the peripheral ANS, depending on a close crosstalk between them were offered. Finally, the administration of drugs that act at the CNS level should be managed by physicians who possess a thorough knowledge of CNS physiology. These results are supported not only by some recent therapeutic trial failures but also by the ongoing iatrogenic neuropharmachologic medication prescribed by doctors seeking to treat depression, sleep disorders, and other psychiatric disorders, whose ANS repercussions are often ignored.

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