

Central Nervous System Circuitries Underlying Two Types of Peripheral Autonomic Nervous System Disorders

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Abstract: The assessment of circulating neurotransmitters: noradrenaline, adrenaline, dopamine, platelet serotonin, plasma serotonin and plasma tryptophan before and after many types of stressor agents and neuropharmacological drugs carried out over the last thirty years allowed us to accumulate information dealing with the central nervous system (CNS) versus the peripheral autonomic nervous system (ANS) interactions in healthy as well as diseased mammals. Furthermore, the accurate knowledge about the CNS circuitry disorders which underlie both the CNS and peripheral clinical syndromes, has allowed us to prescribe successful neuropharmacological therapeutical strategies for many types of illnesses. In addition, the demonstration that the clinical improvement was always paralleled by the normalization of the neurochemical, hormonal, immunological and clinical profiles affords strong support to our point of view. According to all the above, the authors postulate the existence of two types of diseases: type A and Type N, which are underlain by two opposite CNS + ANS disorders. Type A diseases should be associated with the "uncoping stress" syndrome and are underlain by hyperactivity of the adrenocortical glands plus the CNS disorder characterized by the predominance of the C1(adrenergic) + DR(serotonergic) axis over the A5(noradrenergic) + MR(serotonergic) binomial, whereas the type N diseases depends on the opposite profile: "endogenous depression" syndrome. Finally, we quoted exhaustive evidence showing that the well known fading of both the A6(noradrenergic) + C1(adrenergic) CNS nuclei activity occurring during aging is responsible for the ANS + CNS disorder which is similar to that underlying psychosis, Alzheimer, post-traumatic stress disorder and deficit-attention hyperactive disorder.

INTRODUCTION

We have assessed the peripheral autonomic nervous system (ANS) in more than 30, 000 healthy and diseased subjects, throughout the last 30 years. Circulating neurotransmitters [noradrenaline (NA), adrenaline (Ad), dopamine (DA), plasma free serotonin (f-5-HT), platelet serotonin (p-5-HT) and tryptophan (trp)], blood pressure (BP), heart rate (HR), plasma glucose, plasma insulin, plasma cortisol, plasma prolactin and other hormones have been also investigated before and after different types of stressor such as orthostasis, exercise [1-5], and oral glucose tolerance test [6-8]. We have also investigated the effects induced by different types of drugs: clonidine [9-11], sibutramine [12], buspirone [13], tianeptine [14], arginine [15], doxepin [8], dexamethasone [16, 17] on the circulating neurotransmitters of both normal and diseased subjects.

The neurotransmitters have also been investigated during sleep periods [18, 19] in normal and diseased subjects. Finally, the above tests have been carried out during both relapsing and remission periods. The information derived from that research work has allowed us to understand the pathophysiological mechanisms which underlie most type of diseases: gastrointestinal, cardiovascular, endocrinological, neurological, psychiatric and others; and in addition, to be the first to demonstrate the neuroautonomic profiles which

underlie psychosis [20-23], endogenous depression [4, 24], hyperinsulinism [8, 24-31], biliary dyskinesia [32-34], ulcerative colitis [35], infertility [26, 36], duodenal ulcer and gastritis [37, 38], irritable bowel syndrome [39-43], Crohn's diseases [44, 45], pancreatitis [45-48], essential hypertension [6, 49, 50], thrombocytopenic purpura [51], polycythemia vera [52], myasthenia gravis [53], reactive hypoglycemia [8], cardiovascular and pulmonary disorders [53-60], bronchial asthma [61-64], neurological disorders [65, 66], and others. In addition, we demonstrated that the enhanced plasma levels of Ad were associated with both cancer progression and natural killer cells hypoactivity [67-69]. Furthermore, the systematic assessment of the neurochemical plus immunological parameters allowed us to demonstrate that TH-1 and TH-2 autoimmune diseases are underlain by neural sympathetic and adrenal sympathetic predominance, respectively [67]. Finally, in the present review article we will refer to the adequate differentiation of both types of syndromes, which allow successfully treatment with neuropharmacological manipulations of drugs addressed to revert the CNS + ANS disorders.

ANATOMICAL EVIDENCE

The pontomedullary A5 noradrenergic (NA) nucleus is responsible for the activity of the neural sympathetic nervous system [70-72]. This nucleus sends excitatory axons to the lumbar sympathetic acetylcholinergic (ACh) pre-ganglionic neurons located at the spinal intermedio lateral segment [73-75]. Axons of these neurons innervate the somatodendritic area of the NA neurons located at the sympathetic ganglia, which are crowded by nicotinic (excitatory) receptors [76].

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Noradrenergic axons of these neurons integrate sympathetic nerves, which release 80-90% of NA plus 10-20% of DA [77]. Conversely, the medullary C1 adrenergic (Ad) nuclei send glutamatergic axons to the spinal intermediolateral ACh neurons located at the thoracic segment which sends excitatory axons to the adrenal glands that secretes 80% Ad + 10% NA + 10% DA, approximately [70-72, 78-80], which are crowded by excitatory nicotinic receptors [81]. Moreover, the A5(NA) and the C1(Ad) nuclei interchange inhibitory axons [74, 76, 82, 83]. Noradrenaline and adrenaline released from both types of axons act at postsynaptic inhibitory alpha-2 receptors [84] hence, both peripheral sympathetic branches can modulate each other [85, 86]. Besides, those catecholaminergic nuclei send inhibitory axons to the A6(NA) or locus coeruleus pontine nucleus, at which level secrete noradrenaline and adrenaline, respectively. These catecholamines released at the A6(NA) nucleus exert their inhibitory effects by acting at alpha-2 receptors which crowd this nucleus. Furthermore, A6(NA) neurons send direct inhibitory axons to the A5(NA) and modulatory (polysynaptic) drives to the C1(Ad) nuclei [73, 76, 77, 87-93]. However, A6(NA) neurons may also be excited by glutamic acid [89] as well as by ACh axons which arise from the brain cortex and the pedunculo pontine nucleus (PPN), respectively [94, 95]. The former excitatory drive act at the glycine component of the NMDA receptors, whereas the ACh axons act at the muscarinic receptors located at the A6(NA) nucleus [65]. Finally, ACh axons which arise from the medullary vagal complex are also able to excite the A6(NA) neurons [65, 67], during acute parasympathetic rebounds that provoke abrupt inhibitory responses from the A6(NA) axons addressed to restore the ANS acute unbalance episode. This effect is mediated by the release of noradrenaline from the A6 axons at the medullary nucleus tractus solitarii (ACh) [96-98].

PHYSIOLOGICAL EVIDENCE

The A5(NA) and the C1(Ad) nuclei innervate subcortical structures [93], whereas the A6(NA) innervates both the brain cortex and subcortical areas [99]. Hence, this latter nucleus does not display primary (direct) effects on the ANS physiological mechanisms. This phenomenon is consistent with others showing that the number of neurons of the A5(NA) and C1(Ad) nuclei is completed by birth [93, 100-103] whereas the number of A6(NA) neurons do not reach totality until adulthood [104-114]. Furthermore, these neurons fade gradually with aging [104, 107, 115]. This fading is paralleled by the underactivity of the C1(Ad) nuclei in such a way that aging is always accompanied by the progressive predominance of the A5(NA)-neural sympathetic activity. These findings are also consistent with facts showing that most psychiatric disturbances - psychosis [67, 105, 116, 117], attention-deficit hyperactive disorder [65], post-traumatic-stress-disorder [118, 119], and Alzheimer disease [120] - are underlain by the underactivity of the A6(NA) plus the predominance of the A5(NA) neurons that are responsible for the peripheral neural sympathetic system [121-127]. This latter explains the raised NA/Ad ratio always registered in these patients. Finally, we have demonstrated that this neurochemical profile is reversible in endogenous depression patients but not in the other named disturbances [67]. According to all the above, the therapeutical strategy pretending to improve these syndromes should be addressed to revert

the A5(NA) over A6(NA) predominance. In addition to that, it should be expected that the minimization of the A5(NA) activity triggered by this therapy would be paralleled by the disinhibition of the C1(Ad) and the A6(NA) activities [124].

Other physiological evidence showed that the two branches of the peripheral ANS: neural and adrenal sympathetic, are able to antagonize the parasympathetic activity which depends on the release of ACh from these nerves, at visceral targets. This neurotransmitter is not detectable at the peripheral blood because it is fastly destroyed by the acetyl cholinesterase enzyme. Moreover, this neurotransmitter is uptaken by platelets [2, 125]. However, ACh released from parasympathetic nerves is able to act at the nicotinic and muscarinic receptors located at the visceral and muscle levels. Furthermore, parasympathetic nerves interact with sympathetic nerves throughout modulatory rather than a "black vs. white" antagonism [126-129]. Thus, the assessment of the peripheral circulating ACh levels would not afford a useful tool for the understanding of the pathophysiological and/or clinical disorders. Besides, a close cooperation between the peripheral ACh and serotonin neurotransmitters has been demonstrated [2, 125, 130, 131]. This factor affords additional complexity to the management of this circulating neurotransmitter as a useful tool to the understanding of the peripheral ANS mechanisms, as is the case of circulating catecholamines and indolamines.

The circulating serotonin (p-5-HT plus f-5-HT) is released from the enterochromaffin cells located at the small bowel mucosa. Parasympathetic nerves exert an excitatory effect at these cells whereas sympathetic nerves display the opposite activity. Serotonin released to the blood during postprandial periods is partially uptaken by the liver, the lungs and platelets (p-5-HT). However, a small fraction remains free in the plasma (f-5-HT). This plasma serotonin is able to excite the area postrema located at the medullary level (outside the blood brain barrier). This parasympathetic nucleus initiates a cascade of excitatory drive at the CNS which redounds in the additional increase of the enterochromaffin cells activity. Thus, a positive feedback mechanism is triggered. Exacerbation of this peripheral + CNS interaction underlies the pathophysiology of the Bezold Jarisch syndrome [132-135]. This disturbance is successfully treated throughout an adequate neuropharmacological therapy, addressed to enhance the neural sympathetic activity which annuls parasympathetic overactivity [12, 14, 52, 54, 136-139].

PATHOPHYSIOLOGICAL EVIDENCE

The assessment of both circulating neurotransmitters and immunological parameters has demonstrated that almost all diseases are underlain by neuroautonomic plus immunological disorders depending on the neurosympathetic or adrenal sympathetic predominance. The former group is frequently paralleled by the TH-1 immunological profile, whereas the latter is associated with the TH-2 immunological predominance. This adrenal sympathetic group presents with abrupt oscillations between the adrenal sympathetic versus parasympathetic predominance whereas patients affected by neural sympathetic hyperactivity present a rigid profile which shows few and slight alternancy with the parasympathetic ANS profile. These phenomena find explanation in facts

showing that whereas the C1(Ad) medullary nuclei are heavily interconnected with the ACh (medullary) structures, the A5(NA) pontomedullary nucleus sends inhibitory axons to but does not receive from the medullary vagal structures [65, 67, 140, 141]. Furthermore, the flexibility of the Ad vs. ACh medullary interaction is extended to the peripheral adrenergic vs. parasympathetic branches [67, 142]. These physiological plus pathophysiological interactions are monitored by the area postrema. This ACh structure is located at the floor of the IV ventricle and in addition, is not protected by the blood brain barrier, in such a way that the external face is bathed by the blood whereas the internal face interchange axons with other medullary nuclei. Serotonergic 5-HT-3 receptors are excited by the free plasma serotonin (f-5-HT), which is released from the enterochromaffin cells under parasympathetic excitatory drive [131, 143-145]. It functions as an alarm timber which sends signals to the C1(Ad) nuclei. Thus all peripheral parasympathetic overexcitation is fastly annulled by the adrenal glands secretion of adrenaline. In addition, the overexcited C1(Ad) nuclei send inhibitory axons to the A5(NA) neurons [146, 147], thus, the neural sympathetic activity is also annulled in these acute circumstances. This abrupt adrenergic response, registered during acute stress periods is not registered in elderly people because of the hyporesponsiveness of their adrenal cortical glands. These facts explain the different neurohormonal stress profiles registered in young and elderly mammals [3, 16, 17, 148].

In summary, we should understand that the acute stress in young mammals is underlain by raised catecholamines plasma levels + low NA/Ad ratio + raised cortisol plasma levels, whereas in elderly mammals, the acute stress is underlain by moderately raised catecholamines + normal or high NA/Ad ratio + moderately raised cortisol in the plasma, however, it is important to know that both basal noradrenaline and cortisol are permanently raised in elderly people when tested versus young people. The A5(NA) over the C1(Ad) predominance registered in the former explain the above catecholamines profiles, whereas the higher cortisol plasma levels, registered in elderly people depends on the predominance of the median raphe (MR) over the dorsal raphe (DR) serotonergic neurons registered during aging. This MR(5-HT) over DR(5-HT) predominance parallels the A5(NA) over C1(Ad) unbalance [136]. With respect to this, it should be known that the C1(Ad) and DR(5-HT) activities are positively correlated thus, any enhancement of activity of the first is followed by the excitation of the second, because both nuclei interchange excitatory axons. Furthermore, the fading of these two nuclei, registered during elderly fits well with all the above. Moreover, the fact that basal cortisol plasma levels are raised during aging finds explanation in other facts showing that serotonin released at the hypothalamic level is released from the MR(5-HT) rather than the DR(5-HT) axons [136]. The former axons trigger the release of serotonin as a continuous but not intermittent flowing which provokes down regulation of the hypothalamic cortisol receptors because of the sustained basal release of this hormone [136]. This phenomenon is consistent with the non-suppression of plasma cortisol during the dexamethasone suppression challenge registered in elderly people [17]. This disorder is similar to that registered in endogenous depressed patients [10]. Besides, it should be remembered that both

endogenous depressed and elderly people share the same neuroendocrine and neuroautonomic profiles as well as psychotic, post-traumatic stress and attention-deficit hyperactive disorders. All of them present with neural sympathetic over adrenal sympathetic predominance [67]. These pathophysiological disorders are paralleled by the same neurocircuitry disorder: A5(NA) predominance over the C1(Ad) + A6(NA) and MR(5-HT) over DR(5-HT) predominance [65].

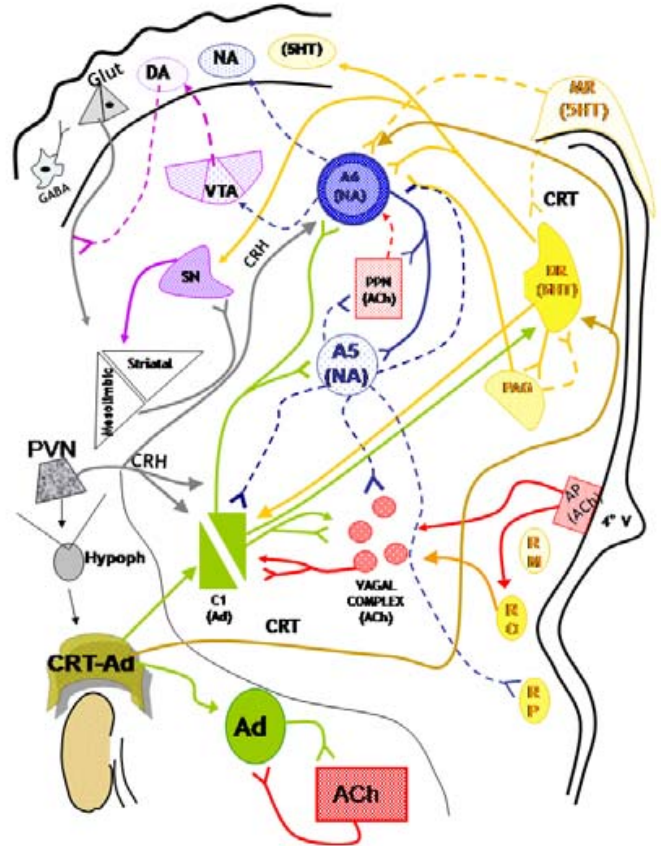


Fig. (1). Adrenal sympathetic activity. This peripheral branch of the autonomic nervous system depends on the secretion of catecholamines by the adrenal gland [80% of adrenaline (Ad) + 20% of noradrenaline (NA) + 10% of dopamine (DA)]. These glands receive excitatory axons from the thoracic presynaptic (ACh) neurons. These ACh-neurons depends on the excitatory drives arising from the C1-Ad medullary nuclei, which in addition send inhibitory axons to both the A5(NA) and the A6(NA) nuclei. Furthermore, these subjects present also, raised levels of plasma cortisol (CRT), which depends of the DR-5HT axons. This serotonergic nucleus interchanges excitatory drives with the C1(Ad) nuclei. Finally, both DR(5-HT) and C1(Ad) axons excite the hypothalamic paraventricular nucleus. Evenmore, CRT crosses the blood brain barrier and excites the DR(5-HT). This positive feedback explains the raised levels of circulating adrenaline and CRT, always registered in these patients. The above anatomical + physiological + pathophysiological mechanisms are reverted by administration of NA uptake inhibitors like desipramine. Finally, the raised levels of Ad and CRT in the plasma are consistent with the bulk of clinical syndromes underlain by the uncoping stress syndrome [67].

THERAPEUTICAL EVIDENCE SUPPORTING THE POSTULATION THAT THERE EXIST TWO TYPES OF DISEASES: NEURAL SYMPATHETIC (N) AND ADRENAL SYMPATHETIC (A)

Type A Diseases (See Fig. 1)

Considering that these diseases are underlain by the adrenal sympathetic overactivity (uncoping stress profile), the therapy should be addressed to enhance neural sympathetic activity; thus the treatment includes the administration of a noradrenaline-uptake inhibitor like desipramine [149-151] in order to enhance the activity of the A5(NA) neurons which are inhibited by both the C1(Ad) and the A6(NA) axons in these patients [152]. These latter nuclei are hyper-excited by the over-release of corticotrophin releasing hormone (CRH) from hypothalamic axons. This phenomenon explains why yohimbine (an alpha-2 antagonist) should be added to desipramine. This alpha-2 antagonist would excite the firing activity of the hypoactive A5(NA) rather than the hyperactive C1(Ad) and/or A6(NA) neurons [153]. Obviously, the administration of yohimbine would act neither at the A6(NA) neurons [154], nor at the C1(Ad) or the DR(5-HT) neurons because all three nuclei are hyper-excited by the CRH released from paraventricular hypothalamic terminals. According to the above, the recovery of the A5(NA) neurons would reduce the C1(Ad) + A6(NA) over-activity, responsible for the hypersecretion of adrenaline plus cortisol [136, 155-159].

Moreover, the DR(5-HT) nucleus interchanges excitatory axons with the C1(Ad) neurons and sends inhibitory axons to the A6(NA) nucleus [88, 160]. In addition, plasma cortisol crosses the blood brain barrier and excites cortisol-receptors located at the DR(5-HT) neurons [67]. Furthermore, serotonin released from the DR(5-HT) axons at the hypothalamic level excites the CRH + ACTH + cortisol cascade [161, 162] that underlies the hormonal branch of "uncoping stress" syndrome, which cooperates with the above explained positive feedback. Summarizing, the inhibition of the hyperactive C1(Ad) neurons would disinhibit the A5(NA) nucleus and in addition, will reduce its excitatory drives to the DR(5HT) nucleus, which would redound in the disinhibition of the A6(NA) neurons [136, 163, 164].

With respect to all the above, it should be known that the raised adrenaline plasma levels registered during the uncoping stress periods are responsible for the TH-2 immunological profile, which always parallels this syndrome that underlies both infectious and malignant diseases during relapsing periods. This neuroimmunological disorder depends on the ability by the raised levels of adrenaline to interfere with the natural killer (NK) cells cytotoxicity against the malignant cells. This phenomenon fits well with the successful therapeutic effects obtained in advanced cancer patients with neuropharmacological manipulations addressed to reduce plasma Ad levels [44, 65, 67, 68, 165-168].

Besides, it is necessary to normalize the sleep disorder which is always present at these circumstances. This target is reached by the administration of clonidine (0.15 mg) plus doxepin (25 mg) or imipramine (25 mg) or clomipramine (25mg) at nocturnal period. The former drug (an alpha-2 agonist) would attenuate the overactivity of the A5(NA) + A6(NA) + DR(5-HT) nuclei triggered by the diurnal pre-

scription (all of them are crowded by inhibitory alpha-2 receptors) whereas the tricyclic drugs would allow the slow plus progressive fading rather than the sudden fall of the above mentioned A6(NA) + DR(5-HT) nuclei [18, 169-172]. These tricyclic drugs are both NA- and 5-HT-uptake inhibitors thus, they would interfere with the abrupt fall of the firing activity of the NA plus 5HT neurons, allowing a gradual and progressive fading of this binomial system [173]. This neuropharmacological manipulation is necessary to elongate the slow wave sleep (SWS) and avoid the short-rapid eye movement (REM) latency always present in both stressed and endogenous depressed patients [174, 175].

Type N Diseases (See Fig. 2)

Taking into account that these diseases are underlain by neural sympathetic predominance plus reduced adrenal sympathetic activity: C1(Ad) + A6(NA) + DR(5-HT), our therapeutic strategy is addressed to revert this neurochemical profile. With respect to this, we prescribe the following treatment: an noradrenaline-uptake inhibitor like desipramine + an alpha-2 agonist such as clonidine, plus physostigmine or rivastigmine (ACh inhibitors, which excite the A6(NA) and the C1(Ad) nuclei but not the A5(NA) neurons) [176-178], plus olanzapine or any other similar drug before breakfast and lunch. In addition, we add doxepin or clomipramine or imipramine before supper and mirtazapine (an alpha-2 + 5HT-2 antagonist) before bed. We will explain the rationality of this therapeutical approach.

Clonidine should inhibit the overactive A5(NA) but not the hypoactive C1(Ad) + A6(NA) neurons thus, desipramine would act at the latter rather than at the former NA nucleus [80, 84, 179-182]. The nocturnal administration of mirtazapine would excite the release of NA + 5-HT from the A6(NA) + DR(5-HT) neurons, respectively, whereas the above mentioned tricyclic (doxepin, imipramine or clomipramine) would facilitate the prolongation of the simultaneous release of NA + 5-HT triggered by mirtazapine. This therapeutical strategy allows the prolongation of the SWS and avoids the short-REM latency. With respect to the above, it should be known that our sleep laboratory demonstrated [18, 24] that the prolongation of the SWS depends on the slow and progressive fading of the noradrenaline circulating levels and that the REM sleep appearance is paralleled by the maximal fall of it. These findings are consistent with others showing that this last sleep period is characterized by the absolute disappearance of the firing rate of both A6(NA) + DR(5-HT) neurons [82, 175, 183]. This explains why all patients affected by the obstructive sleep apnea syndrome present with raised NA/Ad plasma ratio (neural sympathetic overactivity) [24, 174, 183-187]. The above phenomena are consistent with others showing that A6(NA) and A5(NA) axons display a black vs. white antagonism at the upper pharynx and respiratory areas; excitation by the former triggers the opening of it, whereas the latter provokes the closure of this segment [128, 183-187].

NEURAL SYMPATHETIC OR ADRENAL SYMPATHETIC VS. PARASYMPATHETIC INTERACTIONS

Neural sympathetic activity depends on the A5(NA) neurons which send excitatory (glutamatergic) axons to the lumbar sympathetic (lateral) spinal (ACh) neurons. Axons of these latter integrate the sympathetic pre-ganglionic nerves

which synapse at these ganglia. Acetylcholine released from these axons excites post-synaptic nicotine receptors located at these (NA) neurons [76, 127]. Axons of these NA neurons integrate the sympathetic nerves which act at all peripheral and visceral targets. In addition, sympathetic nerves are crowded by muscarinic excitatory plus DA-2 inhibitory receptors in such a way that circulating acetylcholine released from parasympathetic nerves is able to enhance neural sympathetic activity at visceral levels [87, 101, 164, 188-191]. This ACh + NA interaction allows the fast excitation of the neural sympathetic branch. In addition to the above, sympathetic nerves innervate and inhibit the adrenal glands secretion by acting at alpha-2 receptors located at this level [128, 192].

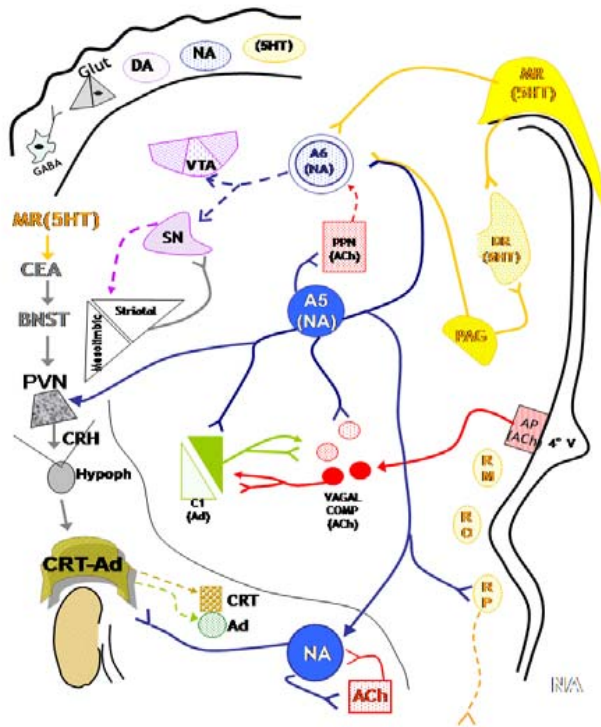


Fig. (2). Neural sympathetic activity. Neural sympathetic activity depends on the sympathetic nerves release of noradrenaline (NA) (90%) + dopamine (DA) (10%). This branch of the peripheral autonomic nervous system (ANS) is positively correlated with activity of the ponto-medullary A5(NA) neurons, which excite the spinal sympathetic neurons and inhibit the C1(Ad) medullary nuclei (responsible for the adrenal glands secretion). In addition, A5(NA) axons inhibit the medullary vagal complex. The absence of C1(Ad) activity redounds in the hypoactivity of the DR(5-HT) neurons. Serotonin released from these axons is the most important factor which initiates and prolongs the corticotrophin releasing hormone (CRH) secretion by the paraventricular nucleus (PVN) at the hypothalamus. The minimization of this factor is consistent with the moderated rise of plasma cortisol (CRT), always registered during neural sympathetic overactivity. In addition to the above, it has been demonstrated that sympathetic nerves inhibit the adrenal glands secretion, directly, by acting at alpha-2 receptors located at these glands. This is consistent with the raised NA/Ad plasma ratio registered in these patients. Furthermore, overactivity of the sympathetic nerves provokes vascular, bronchial, sphincter (gastrointestinal, urinary) contraction always present in this circumstance [67].

Adrenal sympathetic activity depends on the C1(Ad) medullary neurons which send glutamatergic axons to the thoracic sympathetic (lateral) spinal (ACh) neurons [87]. Axons of these neurons innervate the adrenal glands, which are crowded by excitatory nicotine receptors [81]. Adrenaline released from the adrenal glands to the blood stream reaches visceral areas at which level display opposite effects to those triggered by the sympathetic nerves [193]. These effects are mediated by beta-2 receptors, however some areas are crowded by alpha-2 receptors but not by the former [194]. Excitation of alpha-2 receptors by circulating adrenaline provokes cooperator effects with the noradrenaline released from sympathetic nerves. In addition, these nerves are also provided with excitatory alpha-2 receptors [193]. According to all the above, this complex peripheral ANS interaction between the two branches of the peripheral ANS explains the severe pathophysiological disorders arising from the deficit of the adrenal glands secretion, at which circumstances the crosstalk between three factors (neural sympathetic, adrenal sympathetic and parasympathetic) is reduced to two of them [190-196]. Other factors, like the peripheral serotonergic system cooperates with the parasympathetic activity, which triggers the release of 5-HT from the intestinal source and in addition, this latter display an excitatory effect at the area postrema medullary nucleus responsible for the enhancement of the parasympathetic activity. This positive cholinergic plus serotonergic feedback is observed during the called serotonergic syndrome registered in patients affected by the carcinoid syndrome [131-133, 143].

CENTRAL NERVOUS SYSTEM & PERIPHERAL AUTONOMIC NERVOUS SYSTEM PROFILES WHICH UNDERLIE AGING

The underactivity of the adrenal sympathetic system registered during aging converts the trinomial physiological structure which includes neural sympathetic, adrenal sympathetic and parasympathetic branches of the peripheral ANS in a binomial anatomical + physiological “black and white” circuitry. This phenomenon is responsible for the lack of the normal flexibility and compliance which allows the mitigation of the responses to stressor stimuli [108, 194-198].

The A6(NA) and the A5(NA) as well as the C1(Ad) nuclei are excited during acute stress, in such a way that the two sympathetic branches of the ANS might be able to respond in association or dissociation [85]. This compliance allows the attenuation of the stressors effects and avoids the abrupt appearance of the exhaustion periods (uncoping stress). Evenmore, the repetition of controllable stressing periods allows the adaptation to them (coping stress). This physiological capability fades progressively with aging [199-201], because of the progressive minimization of the adrenal glands activity. This peripheral phenomenon finds explanation in the well known reduction of the number of the A6(NA) neurons, which integrate the locus coeruleus pontine nucleus, throughout aging [104]. With respect to the above, it should be remembered that this nucleus interchanges inhibitory axons with the A5(NA) nucleus and in addition sends and receives modulatory axons to and from the C1(Ad) medullary nuclei, which in turn, innervate the A5(NA), at which level provokes inhibitory responses [67].

CONCLUSIONS

The peripheral ANS is modulated by three CNS circuits located at the pontomedullary level: 1) the C1(Ad) vs. the vagal complex; 2) the pontomedullary A5(NA) + C1(Ad) + the vagal complex, and 3) the A6(NA) nucleus which interchanges inhibitory axons with the A5(NA) + C1(Ad) but that is also able to excite or inhibit the latter. The adequate understanding of the above crosstalk is absolutely necessary to treat the ANS disorder underlin diseases. According with this point of view, we postulate the existence of two types of diseases: 1) Type N [underlain by hypoactivity of the A6(NA) + C1(Ad) nuclei plus hyperactivity of the A5(NA) nucleus] which includes: aging, psychosis, endogenous depression, post-traumatic stress disorder, deficit-attention hyperactivity disorder, essential hypertension, hyperinsulinism, multiple sclerosis, myasthenia gravis, and others. This ANS unbalance is associated to TH-1 immunological predominance. 2) Type A diseases underlain by hyperactivity of the C1(Ad) + DR(5-HT) nuclei plus hypoactivity of the A5(NA) nucleus (uncoping stress disorder). This ANS unbalance is associated to TH-2 immunological predominance.

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