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Chapter

# Type 2 Diabetes and Dysautonomy

*Ahmed Anas Guerboub and Ghizlaine Belmejdoub*

## Abstract

Responsibility for the dysfunction of the autonomic nervous system in the genesis or aggravation of cardiovascular and/or metabolic disorders is currently held. Indeed, a significant correlation between sympathetic overactivity and the pathophysiological mechanisms responsible for type 2 diabetes has been proven. Therefore, the treatment of this dysautonomia could improve the management of type 2 diabetes.

**Keywords:** the autonomic nervous system, dysautonomia, type 2 diabetes, insulino-resistance, insulino-secretion

## 1. Introduction

The autonomic nervous system (ANS), the dysregulation of which, called dysautonomia, is a frequent and often unrecognized condition which is accompanied by polymorphic functional manifestations [1]. The exploration of the ANS has gained renewed interest in recent years, due to the demonstration of the major role of its alterations in the genesis and aggravation of several diseases [2]. The importance of type 2 diabetes (T2DM) comes not only from its growing prevalence around the world leading the World Health Organization (WHO) to consider it a significantly expanding epidemic; but also given its human and economic consequences, making it a major public health problem.

## 2. The autonomic nervous system (ANS)

- ANS controls the body's unconscious, vegetative activities. It ensures the normal functioning of vegetative functions (breathing, heart rate, blood pressure, digestion, secretions, body temperature, water balance, etc.), and responds instantly to all physical and emotional demands. It is a system of adaptation of the body to its environment [2].

- The autonomic nervous system consists of two functionally and, in large part, morphologically distinct parts [3]:

  - The orthosympathetic (or sympathetic) system which intervenes in the involuntary activities of the stressful and arousal situations. It is preponderant in the conflicts of the organism with its external environment, when life is threatened. The sympathetic system stimulates all the organs that play a role in the defense response. The sympathetic nerve centers are essentially bulbospinal and their organization is segmental. The preganglionic fibers exit through the

ventral root of the corresponding spinal nerve. They separate to form the white communicating branch which joins the corresponding para-vertebral ganglion. These paravertebral ganglia are united in a chain by inter-ganglionic fibers. The fibers which exit from the paravertebral ganglia join the corresponding spinal nerve by the gray communicating branch to go to the target organ.

- The parasympathetic system which takes care of the involuntary activities of the situations of relaxation and rest. Its nerve centers are located in the brainstem and the sacral marrow. The preganglionic fibers follow the path of the corresponding nerves. They synapse into a pre-visceral or intra-visceral ganglion. The parasympathetic system therefore does not have a structure equivalent to the chain of sympathetic paravertebral ganglia.

- The autonomic or vegetative nervous system is made up of several levels:

  a. Nervous centers located within the central nervous system (medulla oblongata, thalamus and hypothalamus.) and in the spinal cord, constitute the "motor" of the autonomic nervous system.

  b. Peripheral ganglia located on three floors:

     - The first ganglionic stage comprises the para- vertebral sympathetic chain. This chain is located laterally in the spine and extends from the end of the cervical segment to the coccygeal segment. It includes 3 cervical ganglia, superior, middle and inferior through which the sympathetic fibers of the cervical segment pass.

     - A second ganglionic stage consists of the pre-visceral ganglia or plexus. They are less numerous than the paravertebral ganglia. They are more ganglion plexuses than ganglia. They are paired and lateral in the neck (carotid plexus, pharyngeal, ...) and pelvis but single and medial in the thorax (cardiac, pulmonary plexus) and abdomen (solar plexus, lumbo-aortic). At the cervical level, this second stage is associated with the 1st stage.

     - A third lymph node stage includes the visceral or terminal lymph nodes located on the surface or in the thickness of the target organ.

  c. Fibers that connect these levels to each other and to the viscera:

  Between the nerve center and the target organ, the autonomic nervous path is always interrupted by at least one synapse located in a ganglion.

  An autonomous nerve pathway is therefore made up of at least two fibers: the pre-ganglionic fiber and the post-ganglionic fiber.

  The nerve fibers of the autonomic system travel either alongside the fibers of the somatic system (mixed nerves) or independently, along the blood vessels. Norepinephrine is the neurotransmitter at all levels of the sympathetic system, except the ganglionic (acetylcholine) level, while acetylcholine mediates the parasympathetic or vagal system.

- There is a strong interaction between the autonomic nervous system and the endocrine system, especially the hypothalamic–pituitary–adrenal axis. Also,

sympathetic hyperactivity is implicated in various symptoms or pathologies such as essential hypertension [4], obesity [4, 5], permanent resting tachycardia, hyperlipidemia, type 2 diabetes [5], sleep apnea [5] or sedentary lifestyle.

## 3. The ANS measurement methods

- Considered difficult, the assessment of ANS activity has been greatly facilitated by the development of systems allowing non-invasive clinical exploration based mainly on the continuous recording of blood pressure and heart rate by a Holter ECG [6].
- Sympathetic activity can be measured directly by the technique of microneurography which measures muscle sympathetic nerve activity (ANSM) by inserting electrodes into a nerve (usually the peroneal nerve). This technique is very precise and minimally invasive.
- On the other hand, the measurement of the "spill over" of catecholamines is reliable but is not easily applicable due to its very invasive nature. We can also measure catecholamines and their metabolites (metanephrines) in peripheral blood or 24 hours urine, but studies show that plasma catecholamine levels are not sensitive markers of sympathetic activity. Also, they objectify that the urinary catecholamines are not sufficiently sensitive to estimate the sympathetic [6].

## 4. Epidemiological data

- The importance of the type 2 diabetes (T2DM) stems from:
  - Its increasing prevalence throughout the world, around 463 million diabetics in 2019 according to IDF, and to increase to 700 million in 2045.
  - Its association with a remarkable increase in cardiovascular morbidity and mortality.
- The 2000 World Diabetes Congress in Mexico City placed particular emphasis on the metabolic syndrome by sounding the alarm on the impact of such a prevalence on the population. This puts the metabolic syndrome and diabetes far ahead of HIV-AIDS in terms of morbidity and mortality.

## 5. Relationship between type 2 diabetes and ANS

A global approach of the responsibility of a dysfunction of the ANS in the genesis or the aggravation of the 3 main pathophysiological mechanisms of type 2 diabetes, which are insulin resistance, decrease in insulin secretion and hyperglucagonemia, has been attempted, by several studies all over the world especially during the last decades.

a. ANS and insulinoresistance

- Currently there is evidence that sympathetic hyperactivity is responsible for resistance to the action of insulin. Indeed, it can even precede the installation

of this insulin resistance [7]. Activation of adrenergic receptors, in particular β-adrenergic receptors, has been shown to transform the phenotype of muscle cells into insulin-resistant cells [8].

- Variation of adrenaline and noradrenaline may also reduce insulin-induced glucose uptake. The aforementioned metabolic abnormalities are associated with a depletion of capillaries which reduces the supply of nutrients to the muscles which are therefore largely involved in insulin resistance [9, 10].

- In a recent longitudinal study, Flaa A. et al. studied the relationship between sympathetic activity and future insulin resistance in healthy Caucasian subjects with 18 years of follow-up [11]. They found that sympathetic activity was a predictor of insulin resistance as measured by HOMA-IR (Homeostasis model assessement- Insulin resistance: is a method for **assessing** β-cell function and **insulin resistance** (IR) from basal (fasting) glucose and **insulin** or C-peptide concentrations).

- In addition, there is a strong inflammatory activity in abdominal obesity with macrophage infiltration of visceral adipose tissue. These macrophages will be responsible for the secretion of pro-inflammatory factors such as interleukin 6 (IL6) or tumor necrosis factor alpha (TNF alpha) [12]. The secretion of these two cytokines by the visceral adipose tissue in obesity may play a specific role in the development of insulin resistance. Indeed, these factors can activate inhibitory pathways of the insulin cascade which will therefore have less effect on sensitive peripheral tissues (skeletal muscle and liver for example) and therefore induce insulin resistance [13].

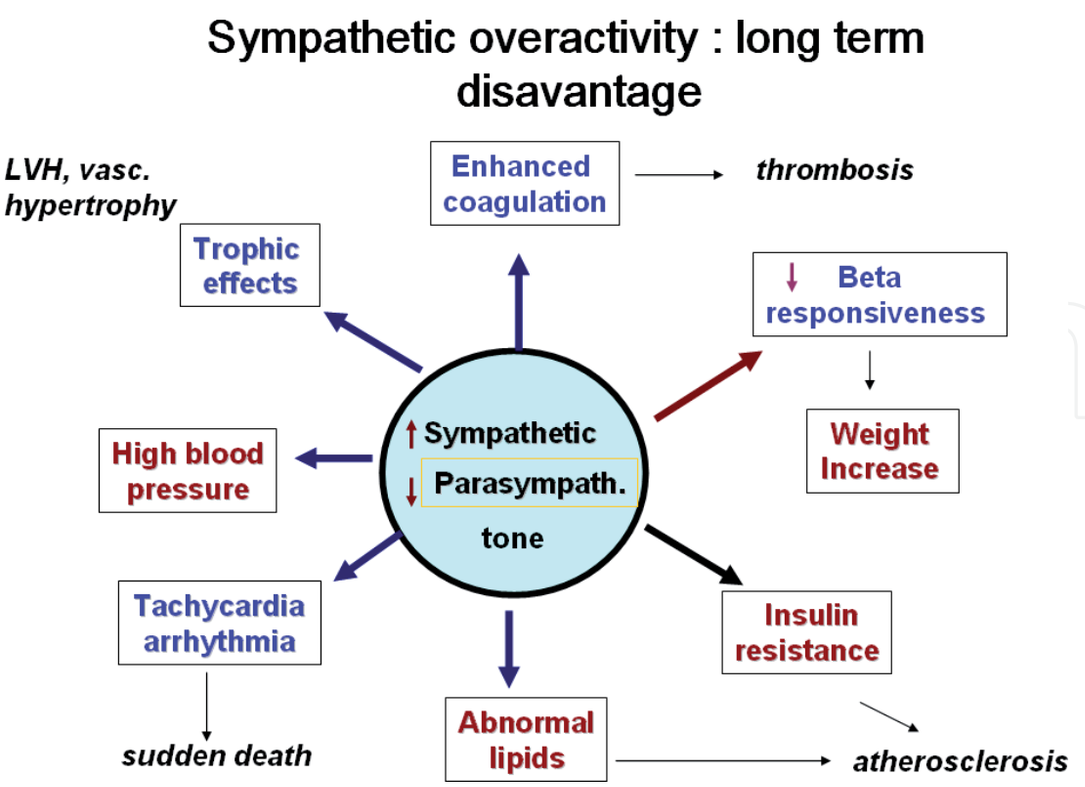


**Figure 1.**
*Schematic representation of the association between sympathic hyperactivity and the different metabolic and cardiovascular pathologies [8]. Sympathetic overactivity is implicated in various symptoms or pathologies such as essential hypertension, obesity, permanent resting tachycardia, hyperlipidemia, type 2 diabetes, sleep apnea.*

- These results provide new information on the pathophysiological mechanisms of insulin resistance, suggesting that sympathetic overactivity may be a predisposing factor for future insulin resistance (**Figure 1**).

b. ANS and insulinosecretion:

There are hormones that are part of the metabolic extension of the sympathetic while others are the metabolic extension of the parasympathetic. Insulin is part of the parasympathetic-vagal tendency.

The vagal deficiency secondary to T2DM is added to the depletion of the beta cells of the islets of Langerhans in the pancreas, thus exacerbating the insulin deficiency of type 2 diabetics [14].

c. ANS and hyperglucagonemia:

There is a microcirculation within the islets of Langerhans. Arterial blood first passes through "β" cells and "δ" cells (somatostatin) before reaching "α" cells which therefore do not respond directly to hyperglycemia. Hyperglucagonemia is secondary on the one hand to a direct stimulatory sympathetic action on "α" cells; and on the other hand, to a vagal deficiency responsible for the lifting of the inhibition on the "α" cells and a decrease in the stimulation of the "β" cells responsible for a decrease in GABA and molecules contained in the granules (Zinc) [15].

## 6. Outlook

To date, little therapeutic benefit has been gained from this information, since centrally acting sympatho-inhibitory drugs and alpha and beta blockers are used in the treatment of arterial hypertension.

Beta blockers are known to make diabetes worse. On the other hand, quite interestingly, drugs having a central sympatho-inhibitory action, such as clonidine and rilmenidine, are neutral or even slightly beneficial in diabetes and the metabolic syndrome.

Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) can be extremely effective in regulating the autonomic nervous system and blood pressure. At the same time, some studies indicate that serotonin-norepinephrine reuptake inhibitors (a SNRI) are even more effective.

These data may also lead to the proposal of sympathetically inhibiting drugs of central action in patients with metabolic syndrome in order to reduce the cardiovascular and metabolic consequences and perhaps even better in the unincorporated phases of the MS hoping to reduce the probability of evolution towards the constituted SM.

## 7. Conclusion

The responsibility of sympathetic dysfunction in the genesis or aggravation of cardiovascular and/or metabolic disorders is currently confirmed.

The consequences could vary depending on the genotypic and phenotypic characteristics of individuals and their environment, this encourages us to always

explore the autonomic nervous system as part of the etiological assessment of the metabolic syndrome in general or of arterial hypertension and T2DM in particular.

The metabolic and functional consequences of ANS dysfunction could have a role not only in the genesis of T2DM but also in the development of complications and in its management.

A predominance of the sympathetic over the parasympathetic is responsible for insulin resistance, impaired insulin secretion and hyperglucagonemia, hence the importance of the exploration of the S.N.A both for screening and for management.

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## References

[1] Low PA, Suarez GA, Benarroch EE. Clinical autonomic disorders: classification and clinical evaluation. In: Low PA, editor. Clinical autonomic disorders. 2nd ed. Philadelphia: Lippincott-Raven; 1997

[2] Low PA. Laboratory evaluation of autonomic function. In: Low PA, editor. Clinical Autonomic Disorders. 2nd Ed. Philadelphia. P: Lippincott-Raven; 1997. pp. 179-208

[3] Grubb BP, Karas B. Clinical disorders of the autonomic nervous system associated with orthostatic intolerance: An overview of classification, clinical evaluation, and management. Pacing and Clinical Electrophysiology. 1999;**22**(5):798-810

[4] Bannister R, Mathias CJ, editors. Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. 3rd Edition. ISBN 0-19-2622196. Oxford: Oxford University Press; 1992

[5] Grassi.G. Differential sympathetic activation in muscle and skin neural districts in the metabolic syndrome. Metabolism. 2009 oct 58(10): 1446-51.

[6] Assessment: clinical autonomic testing report of the therapeutic and technology assessment subcommittee of the american academy of neurology. Neurology 1996; 46: 873-80.

[7] Masuo K. al. Sympathetic nerve hyperactivity precedes hyperinsulinemia and blood pressure elevation in a young, non-obese Japanese population. American Journal of Hypertension. 1997

[8] Palatini P, Julius S. The role of cardiac autonomic function in hypertension and cardiovascular disease. Curr Hypertens Rep. 2009;11:199-205.

[9] Grassi G. al. Differential sympathetic activation in muscle and skin neural districts in the metabolic syndrome. Metabolism. 2009

[10] Lee ZSK. al. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. Metabolism. 2001

[11] Flaa A. al. Increased sympathetic reactivity may predict insulin resistance: An 18-year follow-up study. Metabolism. 2008

[12] Gutierrez and al. Impact of increased adipose tissue mass on inflammation, insulin resistance, and dyslipidemia. Current Diabetes Reports. 2009

[13] Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Letters. 2008

[14] Landsberg L. Insulin-mediated sympathetic stimulation: Role in the pathogenesis of obesity-related hypertension (or, how insulin affects blood pressure, and why). Journal of Hypertension. 2001

[15] Girard J, J-F Gautier. Rôle du glucagon dans la physiopathologie et le traitement du diabète. Médecine des maladies métaboliques. 2016.