Mode of action of mixed patches in neurological diseases due to insufficient secretion of Valentonine and 6-Methoxy-Harmalan by the pineal gland

Application to the treatment of Parkinson's disease

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Summary

The Sleep-Wake system**, which we have just discovered, consists of **3 hormones, secreted simultaneously by the pineal gland**, during the nighttime rest period (see Figure 1): **Melatonin (MLT), the neuroprotective hormone, 6-Methoxy-Harmalan (6-MH), the vigilance and daytime hormone, and Valentonine (VLT), the sleep and nighttime hormone.
*This is a significant scientific advance in the history of medicine. **Indeed, until this discovery, we completely ignored how our organism works (see Annex I), during the 24 hours of a Sleep-Wake cycle (circadian rhythm).***

VLT and 6-MH fully control the functioning of the body by modulating:
*- **the responses of 3 specific neurotransmitter receptors** (α_2 noradrenergic, D_1 dopaminergic, and 5-HT_{2C} serotonergic receptors) at the CNS level.*
*- **secretions from the 7 endocrine glands**: pituitary gland, thyroid, thymus, pancreas, adrenal glands, ovaries and testicles.*

*Among the neurological diseases, due to a deficit in the secretion of these 3 pineal hormones, are**: sleep disorders, nervous breakdowns, Parkinson's disease**, **dementia with Lewy bodies, and Alzheimer's disease.** The treatment of these consists of compensating for these deficits. It is therefore a **replacement therapy**, **with these physiological hormones, completely devoid of adverse effects.***

The transdermal patch**, which we have developed, **supplies the body with quantities of VLT and 6-MH, analogous to pineal secretion**, according to curves of evolution of the plasma concentrations / versus time, of VLT and 6-MH, which are superimposed. So that the body cannot tell the difference between the hormones secreted by the pineal gland and those delivered by the patch**. The treatment includes, at bedtime:
*- **oral administration of a 3 mg capsule of Melatonin**. MLT, thanks to its reducing properties, protects neurons from their destruction by oxygenated free radicals;*
*- **and the application of a mixed transdermal patch**, delivering, during an application period of 8 hours, identical amounts of VLT and 6-MH, included, depending on the neurological condition to be treated and the patient's body weight , between 5 micrograms and 40 micrograms (1 microgram, µg, corresponds to 1 / 1000th of a milligram). **The patch should be removed upon waking, after at least 8 hours of application.***

***In Parkinson's disease**, disorders (tremors, akinesia, rigidity) are associated with a partial and significant destruction of dopaminergic neurons, which can be demonstrated by brain imaging (Dat-scan). Dopamine is the neurotransmitter that allows the transmission of nerve impulses in dopaminergic neurons. But, contrary to popular belief, **the clinical symptoms of Parkinson's disease are not due to a lack of dopamine in dopaminergic neurons, but to a lack of dopaminergic neurons.** The surviving neurons are perfectly operational, with a normal release of dopamine in the synaptic slot, at the place of dopamine D_1 receptors; but, if they are not sufficiently modulated by VLT and 6-MH, they alone are not sufficient to compensate for the incapacity of the destroyed neurons, with the consequence of the appearance of parkinsonian disorders: tremors, akinesia , rigidity.*

***The current treatment of Parkinson's disease by administration of L-dopa, combined with inhibitors of dopa-decarboxylase, and/or various dopamine agonists, is deleterious and completely irrational**. It was designed in total ignorance of the Sleep-Wake system.*
***Among the major and unacceptable drawbacks of this treatment, it should be noted**:*

*- **the uselessness of dopa-decarboxylase inhibitors**, which are of absolutely no use, except for the filing of an intellectual property patent for each dopa-decarboxylase inhibitor;*

*- **L-dopa**, which is both the precursor of dopamine in dopaminergic neurons, and noradrenaline in noradrenergic neurons, **will release as much noradrenaline in the synaptic slots of noradrenergic neurons as dopamine in those of dopaminergic neurons** .*

*- and finally**, the fact of administering L-dopa and dopaminergic agonists, during the 24 hours of the biological cycle, leads to a continuous activation of the dopaminergic receptors of the Substantia nigra, with permanent muscle relaxation**. This dosing regimen goes against the true therapeutic objective, which consists in causing muscle relaxation when the organism is in sleep mode, and, conversely, muscle contraction when it is in wake up mode.*

With mixed transdermal patches, the concomitant administration of VLT and 6-MH is added to the endogenous secretion of VLT and 6-MH, which makes it possible to increase the functioning of the surviving neurons, and to compensate for the loss of D_1 dopaminergic neurons.

***From now on, Parkinson's disease will be treated by application of a mixed patch (VLT + 6-MH),** which will make it possible to deliver to the organism, during the period of application, identical doses of VLT and 6-MH, between 20 and 160 micrograms. The doses administered should be sufficient to allow the surviving neurons to compensate for the incapacity of the destroyed neurons. **However, this treatment will only be fully effective after complete withdrawal from L-dopa and other dopamine agonists** who oppose the therapeutic action of VLT and 6-MH.*

I - Introduction: The Sleep-Wake system in Creation

The Sleep-Wake system consists of 3 hormones, secreted simultaneously by the pineal gland, during the nightly rest period (see Figure 1):

- **Melatonin (MLT), the neuroprotective hormone**, discovered by A.B. Lerner, in 1958;

- **6-Methoxy-Harmalan (6-MH)**, **the vigilance and daytime hormone**, discovered by W.M. Mc Isaac, in 1961;

- **Valentonine (VLT), the sleep and nighttime hormone**, discovered by J-B. Fourtillan in 1994.

The discovery of the Sleep-Wake system is the greatest scientific advance in the history of medicine:

- **first of all because it reveals to us the total regulation of the functioning of our organism**, which, like in most mammals and higher vertebrates, evolves according to a circadian rhythm, of 24 hours. This regulation is fully ensured thanks to only two hormones secreted by our pineal gland: Valentonine (VLT), and 6-Methoxy-harmalan (6-MH). **The mechanism of this regulation of our organism was completely unknown before**. We did not know why, nor how, for 8 hours, at night, our body is in sleep mode, nor why, and how, for 16 hours, after waking up in the morning, it quickly goes into wake up mode (see Annex I). When we switch from one mode to another, at bedtime or upon waking, we observe opposite variations in our major vital functions, such as blood pressure and heart rate, alertness, and muscle fiber contraction state; as well as the triggering of secretions from the 7 endocrine glands which occurs either when our body is in sleep mode, or when it is in wake up mode.

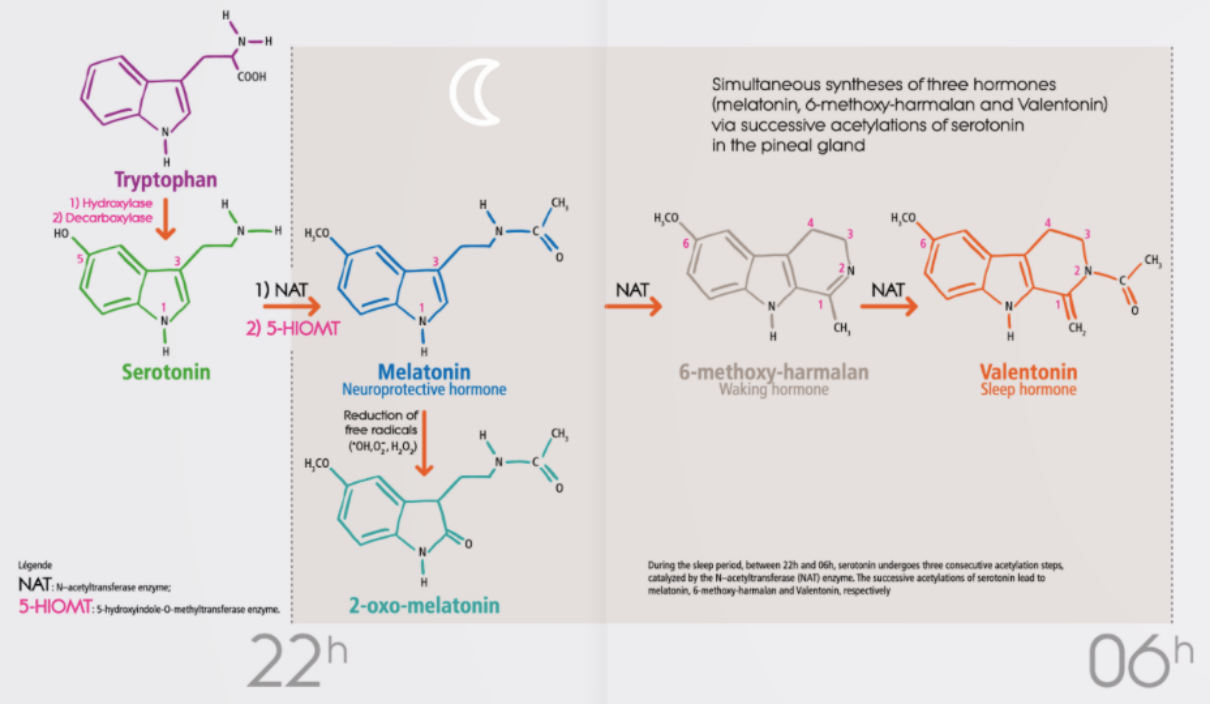
- **because it lets us know the causes of many diseases due to its deregulation**;

- **and because of the innumerable therapeutic applications to which it will give rise**.

Indeed, **only two hormones, Valentonine (VLT)**, the sleep and nighttime hormone, and **6-Methoxy-Harmalan (6-MH)**, the daytime hormone, secreted by the pineal gland for 8 hours, during the rest period (between 10 p.m. and 6 a.m., for a person who usually goes to bed at 10 p.m.), **are sufficient to ensure complete regulation of the organism's psychic and vegetative lives during the 24 hours of nycthemeron**. They are biosynthesized and secreted at the same time as **Melatonin** (**MLT**, see Figure 1, below).

Figure 1

Simultaneous biosyntheses of the 3 hormones of the Sleep-Wake system are carried out in 3 successive acetylation steps, starting from serotonin, under the action of the enzyme N-Acetyl-Transferase (NAT)



II - Kinetics of pineal secretions (figure 2)

We were able to measure the plasma concentrations of VLT and 6-MH, in a healthy subject (male, 61 years, 1m 75, 68 kg), for whom the secretions of pineal hormones are sufficiently high, to be measured with precision and accuracy by using a technique of coupling liquid chromatography with mass spectrometry (LC-SM / SM). From the values observed between 5 a.m. and 6 a.m., just before their secretions by the pineal gland were stopped, we were able to calculate the amounts of VLT and 6-MH secreted between 10 p.m. and 6 a.m., i.e. 30 µg of VLT and 30 µg of 6-MH, in this subject.

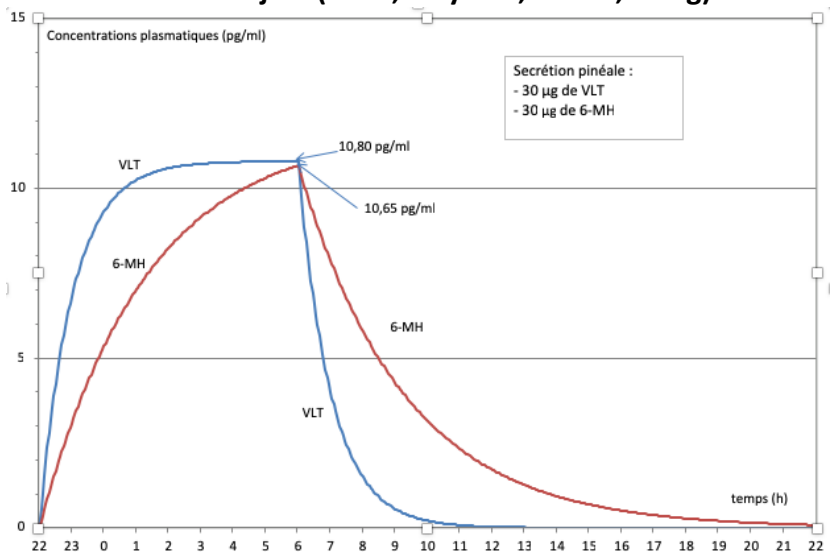
These results show that **the amounts of VLT and 6-MH secreted by the pineal gland, for 8 hours, during the nocturnal rest phase, are identical**. At the same time, the concentrations of VLT in plasma, as well as in its places of action (at the receptors site), are higher than those of 6-MH. **This prevalence is enough to keep our body in sleep mode**.

At the end of the pineal secretions, at 6 a.m., as we can see in our example, in Figure 2, **the concentrations of the 2 hormones are identical** (10.80 pg / ml for VLT and 10.65 pg / ml for 6-MH). **This coincides with the body's transition from sleep mode to wake up mode**.

Then, in a few minutes, **after the secretion of pineal hormones has stopped**, the elimination of VLT being rapid (elimination half-life equal to 0.70 h), **the concentrations of 6-MH**, whose elimination is much slower (elimination half-life equal to 2.27 h), **become prevalent, so that our organism quickly goes into wake up mode.**

Figure 2

Changes in plasma concentrations of VLT and 6-MH, versus time, in one subject (male, 61 years, 1m 75, 68 kg)



Note: We measured the concentrations of 6-MH and VLT in more than 300 subjects, between 38 and 93 years of age, who suffered from one of the 4 pathologies due to a deficit in the secretion of pineal hormones (sleep disorders, nervous breakdowns, Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease), and in healthy subjects. **The results show that, with the exception of a healthy subject (example in figure 2) who secretes 30 µg of VLT and 30 µg of 6-MH, all the others have pineal secretions of less than 5 µg of VLT and 5 µg of 6-MH.**

III - Modes of action of VLT and 6-MH

Reference: see the following videos on the Fonds-Josefa.org website: by clicking on the following link: **"*The Sleep-wake system in Creation*"** and *"The proof in 3D"*

Depending on whether our body is in sleep mode, for 8 hours, or in wake-up mode, for 16 hours, the VLT and 6-MH completely control the functioning of the body by modifying (see Figure 3, below):

1- The responses of 3 specific receptors for neurotransmitters, at the level of the CNS, which regulate the major vital functions:

- α_2 **noradrenergic receptors**, which regulate the cardiovascular system (BP and HR);

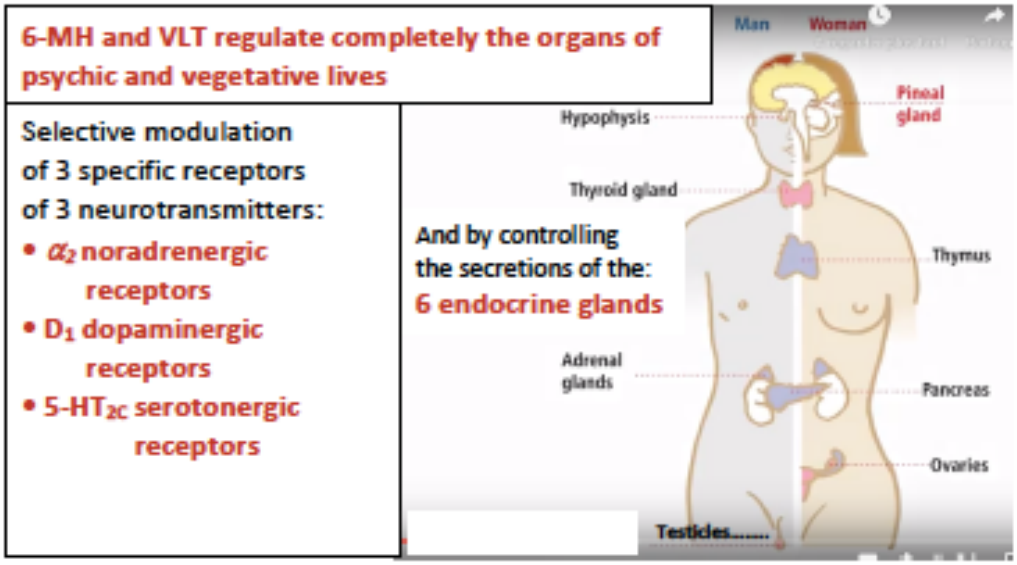
- **D_1 dopaminergic receptors**, which regulate the state of contraction of skeletal muscles;

- **5-HT_{2C} serotonergic receptors**, which regulate vigilance.

2- Secretions from the endocrine glands, such as the secretions of thyroid hormones by the thyroid gland, cortisol by the adrenal glands, estrogen hormones (estradiol, estrone) by the ovaries, androgenic hormones (testosterone) by the testicles, and production of lymphocytes by the thymus, etc.

Figure 3

Valentonine and 6-Methoxy-harmalan provide total regulation of the functioning of the organism during the 24 hours of the nycthemeron



VLT and 6-MH do not bind directly to the protein recognition sites of receptors for neurotransmitters or liberins (see Figures 5 and 6, below), but modulate their responses to these activators (direct acting agonists), by amplifying them, in the case of VLT, or by reducing them (antagonists), in the case of 6-MH, everywhere in the body.

This central regulation of psychic and vegetative lives, controlled by VLT and 6-MH, is carried out in two ways:

1- By modulating the responses of neuronal receptors of neurotransmitters

Three specific receptors are concerned. They are located on inhibitory neurons, whose neurotransmitters are:

- Serotonin, a neurotransmitter of vigilance at the **5-HT_{2C} serotonergic neurons**: **VLT** maintains **sleep** during nighttime, while **6-MH increases wakefulness** during daytime;

- Dopamine, the neurotransmitter of **muscle contraction** and movement control, at the place of **D_1 dopaminergic neurons: VLT** causes **muscle relaxation** during nighttime, while **6-MH** allows **muscle contraction** during daytime;

- Noradrenaline, a neurotransmitter of the cardiovascular system that regulates **blood pressure, and heart rate,** at the place of **α_2 noradrenergic neurons: VLT reduces BP and HR** during nighttime, while **6-MH increases BP and HR** during daytime.

As can be seen in Figure 4, and Figures 5-1, 5-2, and 5-3 (example of the analogy of stereochemical configurations of dopamine, neurotransmitter of dopaminergic neurons, and 6-Methoxy-Harmalan), the stereochemical configurations of VLT, 6-MH, and the three neurotransmitters are identical, in particular with regard to their molecular dimensions (see video: ***Analogy of the stereochemical configurations of VLT and 6-MH and of the 3 neurotransmitters***). They correspond to the steric configurations of the protein sites of recognition of the 3 receptors, which allow them to be placed in the immediate vicinity of these, and to modulate their responses to neurotransmitters, by increasing or decreasing them.

Figure 4

Analogies of stereochemical configurations and molecular dimensions of 3 neurotransmitters, Valentonine and 6-Methoxy-harmalan

Valentonine and 6-methoxy-harmalan
modulators of 5-HT_{2C}, α_2, and D_1 receptors

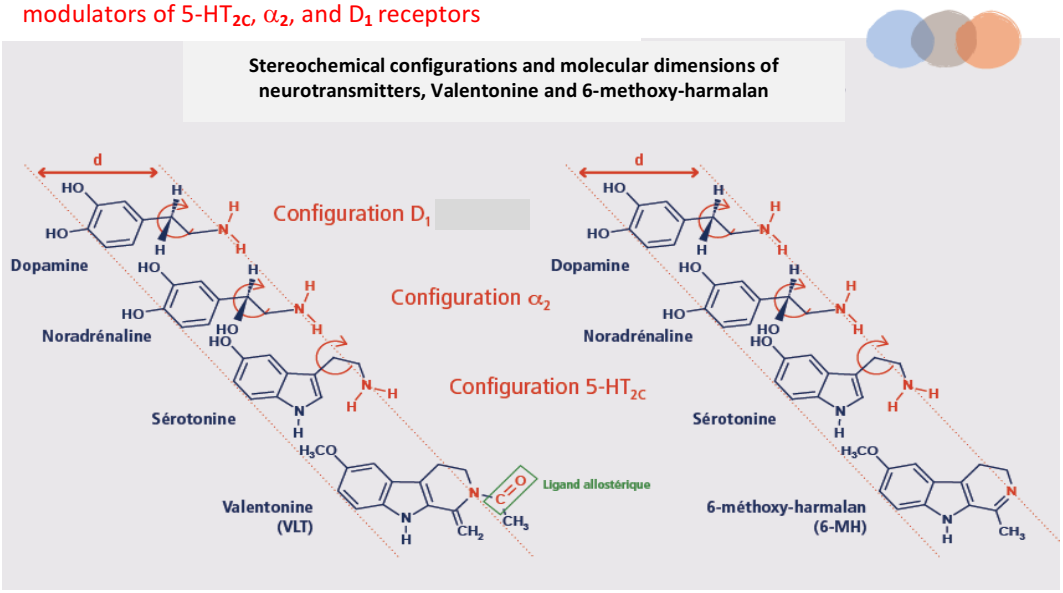


Figure 5-1

Analogies of the stereochemical configurations of dopamine and 6-methoxy-harmalan

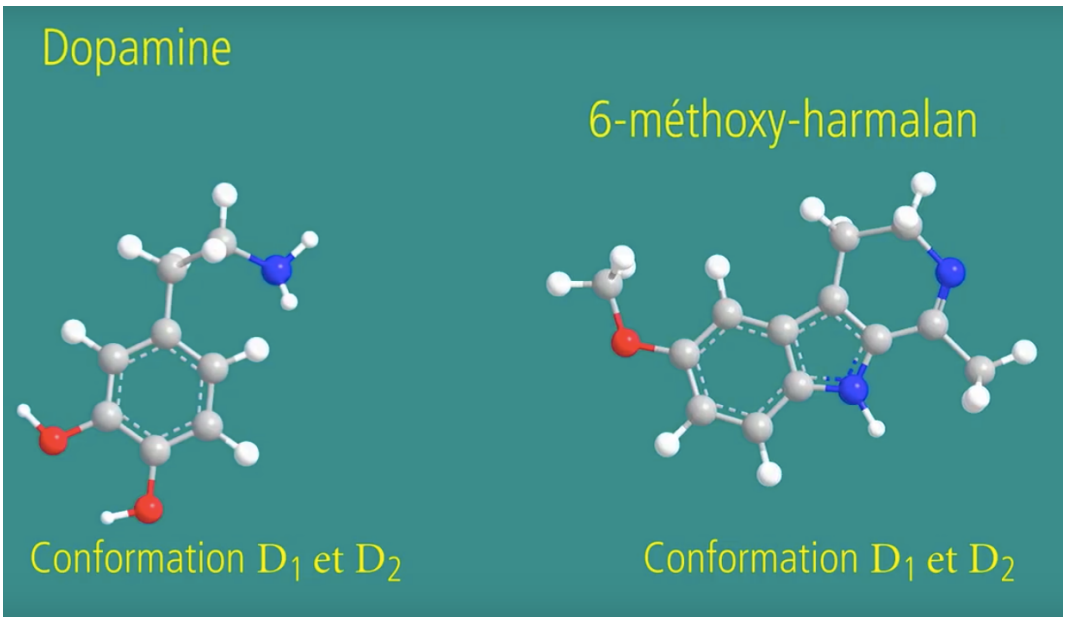


Figure 5-2

Perfect overlays of the 2 skeletons and the nitrogen poles (N) dopamine and 6-methoxy-harmalan

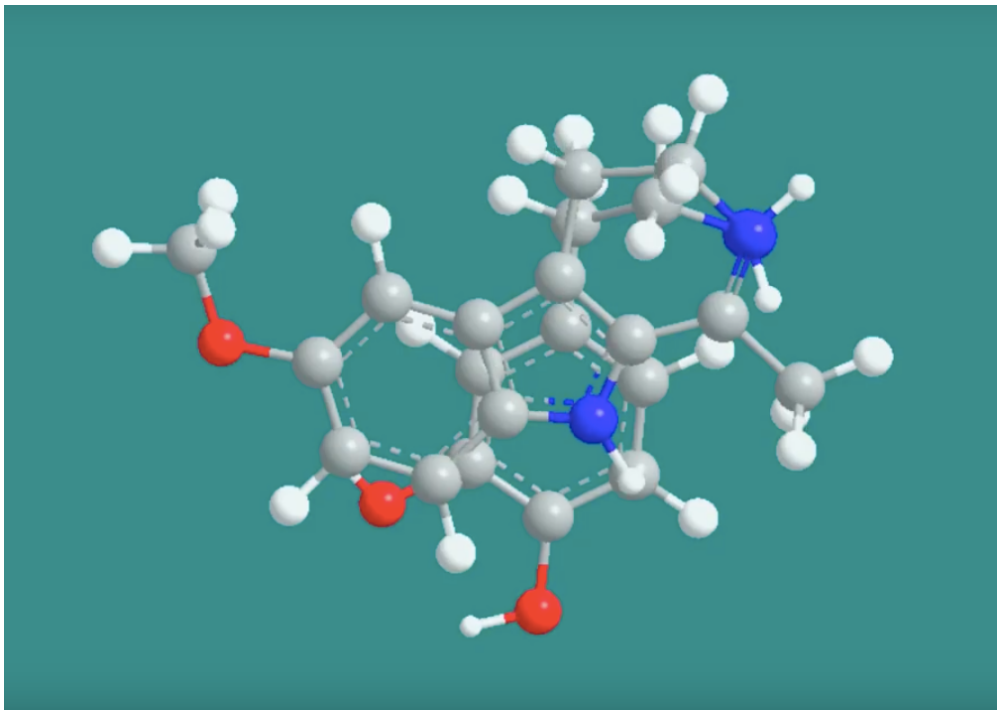
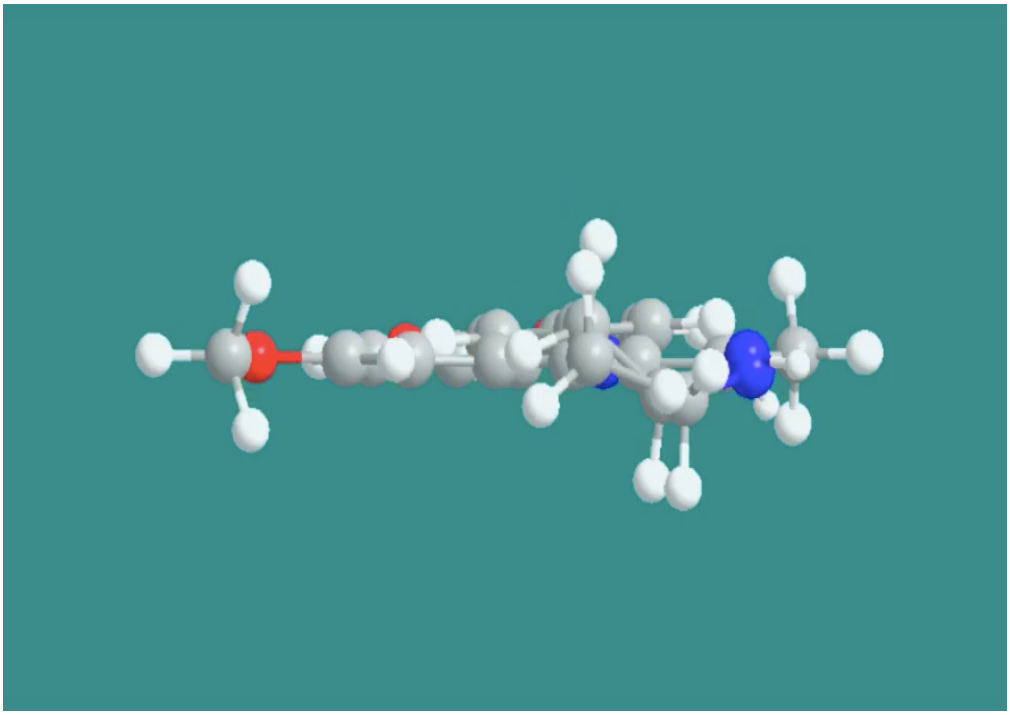


Figure 5-3

Analogies of 3D spatial conformations of dopamine and 6-Methoxy-harmalan



So :

- by changing their spatial structures ("allosteric deformations"), **VLT increases the sensitivities of these 3 specific receptors** (5-HT_{2C} serotonergic, D_1 dopaminergic, and α_2 noradrenergic receptors) **to their respective neurotransmitters**. This results in activation of these receptors; **which results in an increase in the transmission of nerve impulses in these inhibitory neurons**;

- by preventing, by competitive antagonism, part of the neurotransmitter molecules from reaching their action sites (protein recognition sites for each of the 5-HT_{2C}, D_1 and α_2 receptors), **6-MH decreases the responses of these 3 specific receptors to their respective neurotransmitters**. This results in deactivation of these receptors**; then consecutively in a reduction in the transmission of nerve impulses in these inhibitory neurons**;

It will be noted that the modes of action of VLT and 6-MH on the receptor responses are different, and that the amplitude of the responses varies as the algebraic difference in the concentrations of these 2 hormones in the immediate vicinity of the receptors. As we have seen previously, at the end of pineal secretion, the concentrations of VLT and 6-MH are identical. It is precisely at this time that our body changes from sleep mode to wake up mode.

Example of D_1 dopaminergic receptors

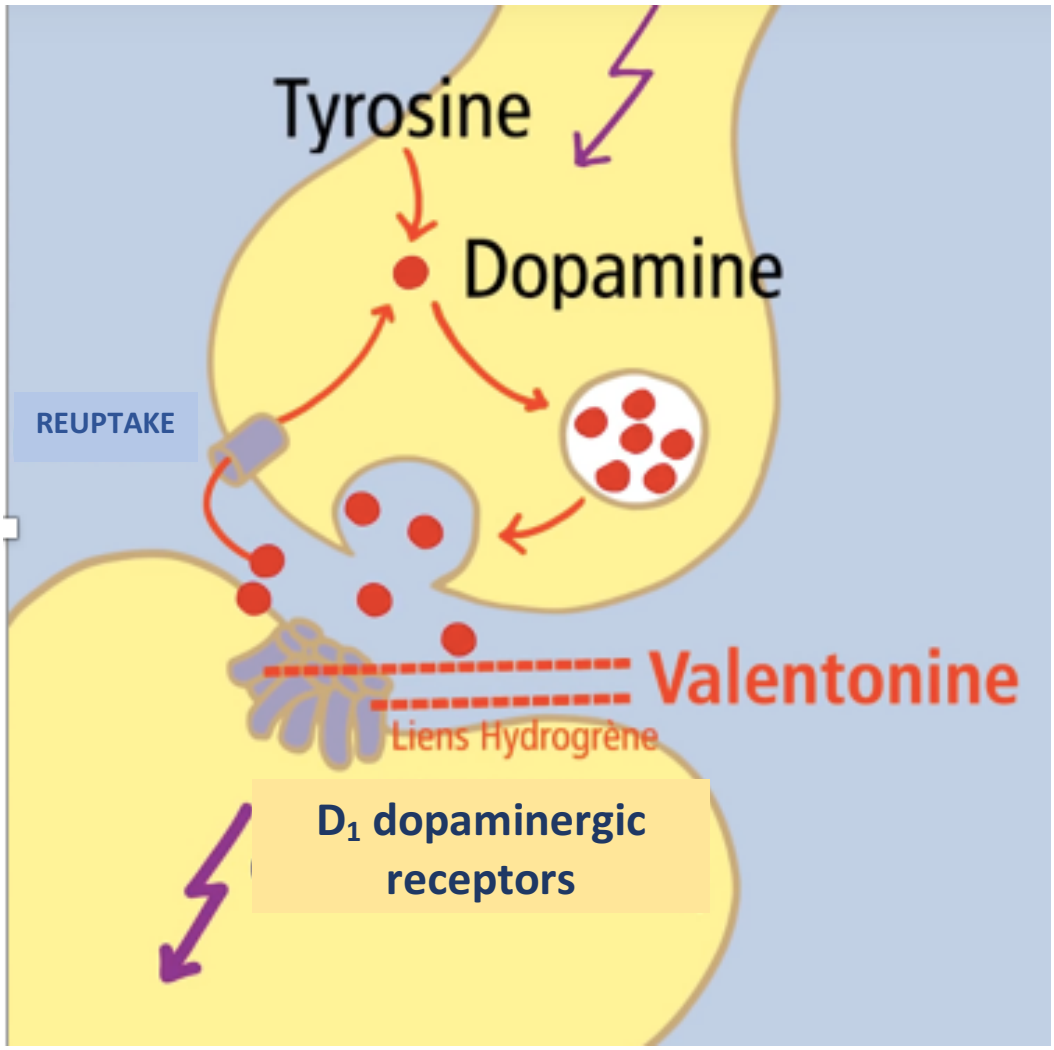
Take the example of D_1 dopaminergic receptors, located in the striated gray nuclei and the Substantia nigra:

- When the body is in sleep mode, the allosteric activation of D_1 dopaminergic receptors by VLT causes muscle relaxation.

Thanks to its acetyl group (allosteric ligand fixed on the nitrogen atom N of VLT), VLT establishes chemical interactions (hydrogen bonds between the carbonyl group **C=O** of VLT and the group **NH** of peptide bonds **-CO-NH-** of the complementary protein sites of D_1 dopaminergic receptors. The deformation of the dopaminergic receptor D_1, which results therefrom, increases its sensitivity to dopamine, which causes its activation and causes muscle relaxation (see Figure 6);

Figure 6

Thanks to its acetyl group CH_3-CO (allosteric ligand), Valentonine causes a deformation of the D_1 dopaminergic receptor which makes it more sensitive to dopamine

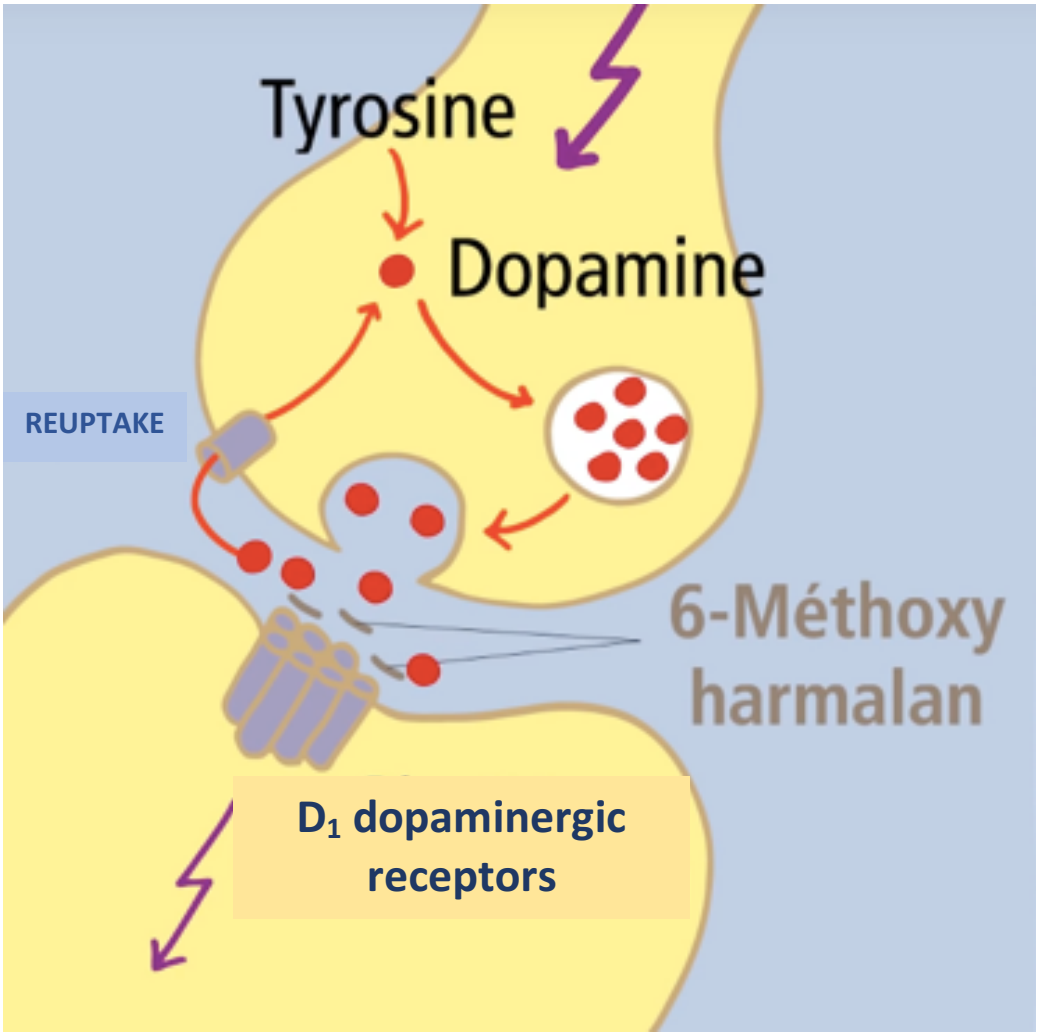


- When the organism is in wake up mode, a competitive antagonism between 6-MH and dopamine causes muscle contraction.

By preventing part of the dopamine molecules from accessing their binding sites on D_1 dopaminergic receptors, 6-MH reduces their stimulation by antagonism towards dopamine, which leads to muscle contraction (see Figure 7), .

Figure 7

6-MH antagonism towards dopamine at the dopamine D_1 receptor site



Modulations of the responses of 5-HT_{2C} serotonergic receptors and of α_2 noradrenergic receptors are carried out in an identical fashion.

Note: It should be understood that the transmissions of nerve impulses in the different types of neurons, as well as the quantities of neurotransmitters released in the synaptic slots, at the neuro-neuronal junctions, are kept constant during the 24 hours of the nycthemeron**. Thus, the regulation of our organism, during the 24 hours of the nycthemeron, is carried out only by the interventions of VLT and 6-MH, the pineal modulating hormones, on their specific receptors.**

2- By increases in the hormonal secretions of the endocrine glands, consecutively to the activations of the pituitary receptors of the liberins.

Liberins are factors that release pituitary hormones, formerly known as "releasing factors". These are hormones produced by different nuclei of the hypothalamus, which act on the pituitary gland. VLT and 6-MH control the secretions of the endocrine glands by modulating the response of pituitary receptors to liberins. Among the pituitary receptors of liberins, we should mention:

- **TRH** (Thyreotropin-Releasing Hormone), the thyreotropic hormone, ultimately intended for the thyroid, which activates the pituitary secretion of **TSH**, thyreostimulin, which, in turn, **will stimulate the secretion of thyroid hormones by the thyroid gland, as well as the pituitary secretion of Prolactin.**

- **CRH** (Corticotropin-Releasing Hormone), a corticoliberin, ultimately intended for the adrenal glands, which will activate the secretion of **ACTH**, the corticotropic hormone, or adrenocorticotrophin, by the pituitary gland. ACTH is a stimulin which, in turn, activates the secretion of **glucocorticoids (Cortisol, Aldosterone**, etc.) by the adrenal glands.
- **GHRH** (English: Growth Hormone Releasing Hormone), or somatoliberin, stimulates the pituitary secretion of growth hormone, **GH** (Growth hormone), also called somatotropic hormone **STH**, which stimulates cell growth and reproduction in humans.

Liberins	Pharmacological actions	Actions of VLT or 6-MH
Thyreoliberin TRH Thyreotropin-Releasing Hormone	- ↑ secretion of TSH - ↑ secretion of Prolactin	- ↓ secretion of thyroid hormones by VLT - ↓ milk synthesis by VLT
Corticoliberin CRH Corticotropin-Releasing Hormone	- ↑ secretion of ACTH Adreno Cortico Trophic Hormone	- ↓ secretions of cortisol and aldosterone by VLT
Somatostatin	- ↑ secretion of STH (GH) Somatotropic Hormone (Growth Hormone)	- ↓ cellular growth and reproduction by VLT

- **GnRH** (Gonadotropin-Releasing Hormone) which will activate the secretion of gonadostimulins, **LH** (Luteinizing Hormone) and **FSH** (Folliculo Stimulating Hormone), two **gonadotropins** including the function is to stimulate the secretion of the hormones **estrogens** (estradiol and estrone), **progesterone**, and **androgens** (testosterone) by the ovaries and the testicles.
- and **various liberins**, of hypothalamic origin, which will activate the secretion by the pituitary gland of directly "operational" hormones, such as **Oxytocin** (during uterine contractions of childbirth), **Prolactin**, and **Vasopressin** (to regulate blood pressure by its antidiuretic action).

The modulations of secretions from the endocrine glands by Valentonine and 6-Methoxy-Harmalan are effected by antagonism of the pituitary receptors of liberins (TRH, GHRH, CRH, GnRH, ...). Most often, the hormonal secretions of all the endocrine glands are reduced during the nighttime.

IV - Treatment of neurological affections due to a deficit in secretions of the pineal hormones

References: see the following 4 videos on the Fonds-Josefa.org website (click on the links):
- « ***Sleep disorders and their treatment*** » ;
- « ***The causes of depressions and their treatment*** » ;
- « ***The causes and the treatment of Alzheimer's disease have finally been discovered*** »
- « ***The true causes and the treatment of Parkinson's disease*** ».

Sleep disorders, **nervous breakdowns**, as well as **neurodegenerative affections** of the **Alzheimer's disease** type, **are,** mainly, **due to insufficient secretions of the 3 pineal hormones**:

- **Melatonin (MLT**), the neuroprotective hormone that reduces oxygen free radicals that destroy neurons during the nighttime rest period;

- **6-Methoxy-Harmalan (6-MH)**, **the hormone of daytime**, which maintains **the waking state** and the performance of **cognitive functions**, by reducing the stimulation of serotonergic receptors 5-HT_{2C}, by serotonin, **contraction of muscle fibers**, reducing the stimulation of dopamine D_1 receptors, by dopamine, and **increases blood pressure and heart rate**, reducing the stimulation of α_2 noradrenergic receptors, by noradrenaline, **during the period of activity;**

- Valentonine (VLT), the hormone of nighttime, which maintains **the sleep mode** by increasing the stimulation of the serotonergic receptors 5-HT_{2C}, by serotonin, allows **the relaxation of the muscular fibers**, by increasing the stimulation of the dopaminergic receptors D_1, by dopamine, and **reduces blood pressure and heart rate,** increasing the stimulation of α_2 noradrenergic receptors, by noradrenaline, **during the nighttime rest period.**

Transdermal administration of identical doses of VLT and 6-MH, between 10 and 40 µg, in the form of patches (mixed patches), applied at bedtime and removed in the morning upon waking, will restore proper functioning of the organism, concerning, among other things, nocturnal sleep, memory, vigilance, physical tone, and cognitive functions during daytime.

V - Parkinson's disease and its treatment

Reference: see the following video on the Fonds-Josefa.org website (click on the link):
- " ***The true causes and the treatment of Parkinson's disease*** "

1- The causes of Parkinson's disease

Parkinson's disease is due to a significant destruction of dopaminergic neurons of the extrapyramidal system, located in the striated gray nuclei and the Substantia nigra. This destruction is mainly due to **neurotoxic metals** such as **aluminum** from vaccines and gastric acid dressings, which contain aluminum hydroxide $Al(OH)_3$ or aluminum phosphate $AlPO_4$, **mercury** from dental amalgams, and **lead**. It is also due to certain neurotoxic chemical agents (glyphosate, rotenone, …), used in agriculture, or even to **electromagnetic radiation**.

Neurologists and other neuroscientists, who did not yet know the existence of the 2 pineal regulatory hormones, Valentonine and 6-Methoxy-Harmalan, completely ignore the mechanism by which nerve impulses are transmitted in dopaminergic neurons, which is implemented in the alternate processes of relaxation, during the period of nighttime, then of contraction of the muscular fibers, during the period of daytime.
They noted, by cerebral imagery, it is an acquired fact, that the parkinsonian disorders are associated with a partial, important destruction, of the dopaminergic neurons, essentially localized in the black substance (Substantia nigra), which are very few, approximately 400 000, in comparison of tens of billions of noradrenergic and serotonergic neurons.

Neurotoxic metals, like aluminum, mercury and lead, are not only concentrated in the Substantia nigra, they are distributed throughout the brain. But it must be understood that when these metals destroy 300,000 serotonergic or noradrenergic neurons out of several tens of billions, they do not disturb the functioning of these neurons too much, while when they destroy 300,000 dopaminergic neurons out of 400,000 present in the Substantia nigra, is 75 per cent of the dopaminergic neurons that are destroyed. Under these conditions, only 25 per cent of surviving dopaminergic neurons remain, the functioning of which will depend on the quantities of VLT and 6-MH secreted by the pineal gland overnight.
Dopamine is the neurotransmitter that allows the transmission of nerve impulses in dopaminergic neurons (see the **Book**, pages 143 to 150, the **Brochure**, DIA 49).

In Parkinson's disease, clinical symptoms (tremors, akinesia, rigidity) appear when the amounts of VLT and 6-MH secreted by the pineal gland are insufficient for the surviving neurons, alone, to be able to compensate by their functioning, the lack of functioning of the destroyed neurons.

Liberated in the synaptic slot, during the propagation of impulses in neurons, dopamine will bind to protein recognition sites of dopaminergic receptors to activate them, and thus ensure the transmission of impulse.
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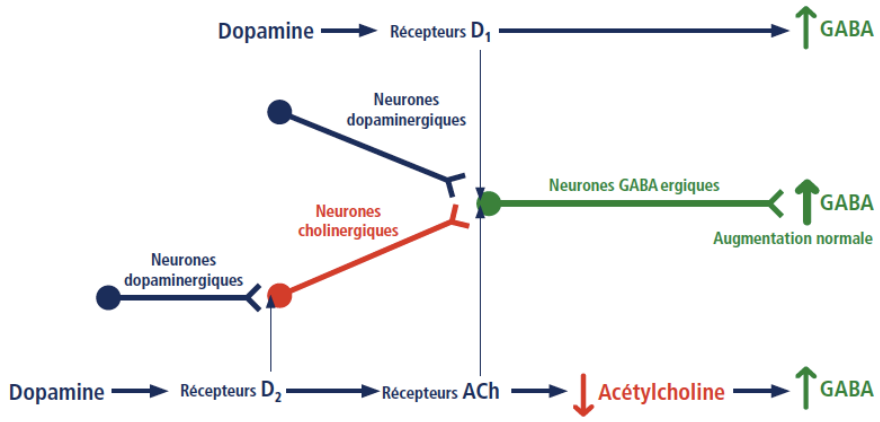
2- The functioning of the extrapyramidal system, and the control of motor skills and movements.

The mechanism, in alternation, of relaxation, during nighttime, and of contraction, during the daytime, of muscle fibers, consists in a **modulation of the activity of D_1 dopaminergic receptors** by VLT and 6-MH. As shown by a binding study, we have carried out with VLT and 6-MH, which demonstrated us that these 2 hormones only modulate the activity of D_1 dopaminergic receptors, which are directly connected to GABA-ergic neurons (see Figure 8), without affecting the dopamine D_2 receptors.

Figure 8

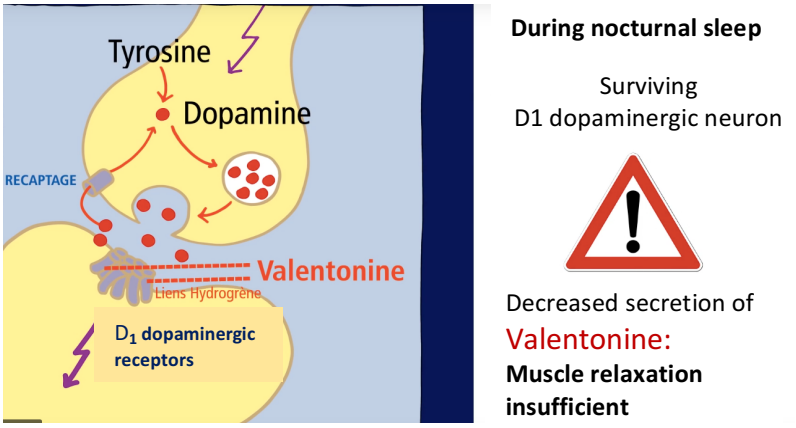
Direct connection between D1 dopaminergic neurons and GABA-ergic neurons



- **Valentonine causes activation of D_1 dopaminergic receptors**, by allosteric deformation (see paragraph IV, and Figure 9); which makes them more sensitive to dopamine. **This activation of D_1 dopamine receptors, which takes place without modifying the dopamine concentrations in the synaptic slot,** results in the relaxation of muscle fibers during sleep-time, when the organism is in sleep mode.

Figure 9

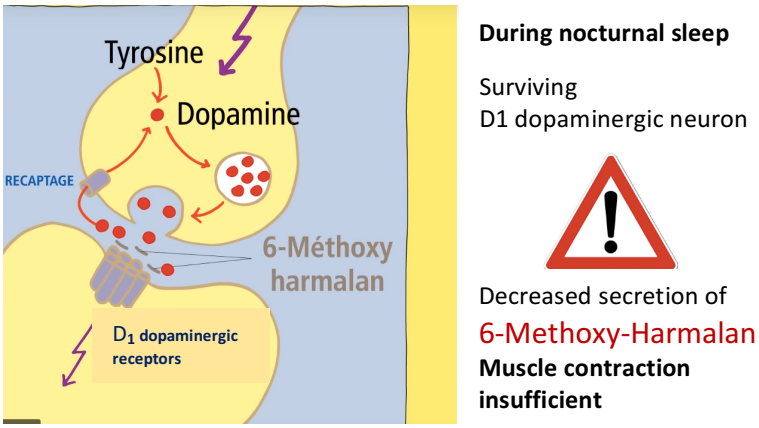
In Parkinson's disease, during sleep-time, the concentration of VLT, at the level of the synaptic slots of the surviving D_1 dopaminergic neurons, is insufficient to compensate for the inability of the destroyed neurons



- **6-Methoxy-Harmalan**, due to its stereochemical configuration analogous to that of dopamine (see paragraph IV, and figure 10), will be placed at the D_1 dopaminergic receptors and prevent, by simple antagonism, part of some molecules of dopamine to reach the active sites of these receptors. **It thus deactivates D1 dopaminergic receptors**, which results in a contraction of muscle fibers during daytime, when the body is in wake up mode. **This deactivation is always carried out without modifying the dopamine concentrations in the synaptic slot.**

Figure 10

In Parkinson's disease, during daytime, the concentration of 6-MH, at the level of the synaptic slots of the surviving D_1 dopaminergic neurons, is insufficient to compensate for the inability of the destroyed neurons



This extremely subtle mechanism was completely unknown until the discovery of the Sleep-Wake system. Since the scientists knew that Parkinson's disease was due to the destruction of dopaminergic neurons, they imagined administering L-dopa to increase dopamine concentrations in the striated gray nuclei and the Substantia nigra, in order to fairly simplistic, as it must be admitted, to increase the transmission of nerve impulses in dopaminergic neurons.

However, **Parkinson's disease is not due to a lack of dopamine in dopaminergic neurons, but to a lack of dopaminergic neurons,** which is not at all the same thing. Indeed, the release of dopamine in the synaptic slots of the surviving dopaminergic neurons (phenomenon of exocytosis), triggered by nerve impulses, is completely normal.

In reality, parkinsonian disorders are due to a lack of the 2 regulatory hormones, Valentonin and 6-Methoxy-Harmalan, the concentrations of which, at the place of the surviving dopaminergic neurons, are insufficient to ensure, by themselves, the alternation of dopaminergic processes of muscle relaxation, during the 8 hours of sleep mode, and of muscle contraction, during 16 hours of wake up mode (see Figures 9 and 10).

Increasing dopamine levels, for surviving dopamine neurons, makes no sense, especially since neurologists administer it 24 hours a day.

The administration of dopamine in the form of L- dopa, or dopaminergic agonists, which act for 24 hours, as well as the implantation of electrodes in the brain at the place of the dopaminergic neurons of the Substantia nigra, for the purpose of increasing the transmission of nerve impulses are therefore not valid solutions. These treatments are doomed to failure, all the more so that with these treatments an activation of the dopaminergic neurons is carried out for 24 hours, whereas they should only be activated at nighttime, when the organism is in sleep mode. So we're only dealing with part of the problem, with a lot of side effects, due to the lack of specificity of dopamine and dopamine agonists.

It should therefore be remembered that **Parkinson's disease is not due to a lack of dopamine, but to simultaneous lack:**

- **dopaminergic neurons**, which have been destroyed mainly by heavy metals, **aluminum of vaccines** and **antacid gastric dressings**, and 2 other heavy metals such as **mercury**, **lead**, as well as by external agents (pesticides, especially products used in agriculture, neurotoxic solvents), and exposure to **electromagnetic radiation waves**, etc.;

- **and 2 pineal regulatory hormones: VLT, and 6-MH,** when the secretions of these two hormones are no longer sufficient for the surviving neurons to be able to compensate for the destroyed neurons.

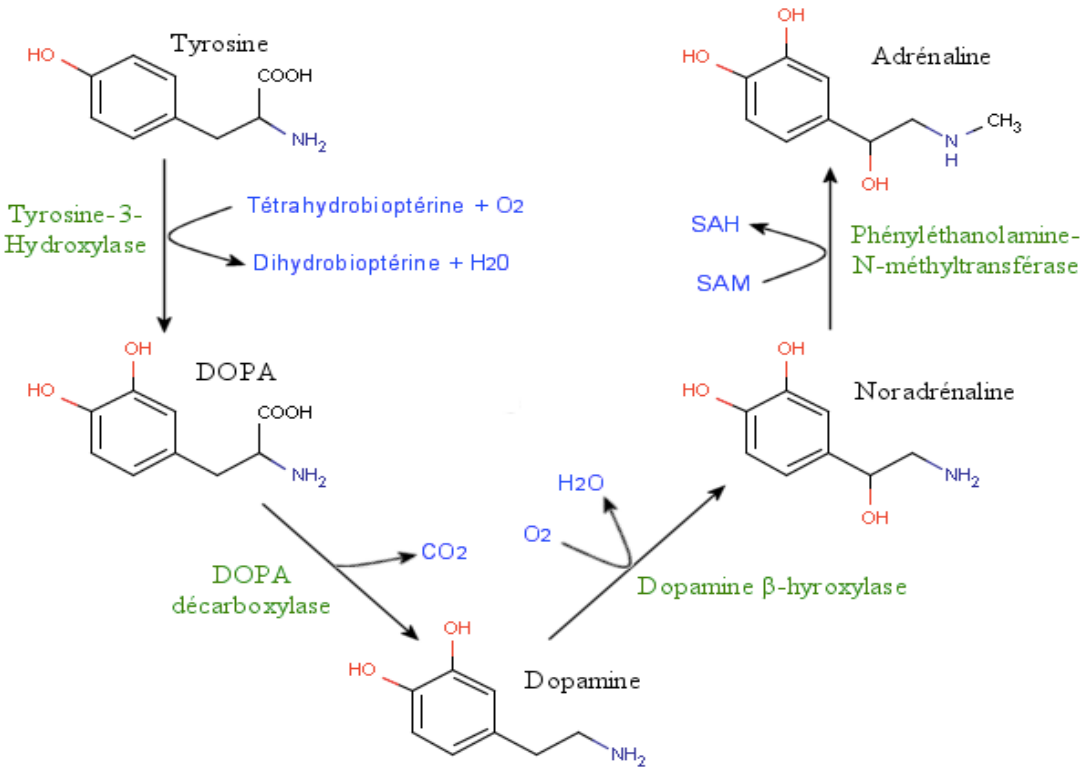
The discovery of this mechanism of regulation of the dopaminergic system of contraction / relaxation of muscle fibers, justifies the **replacement therapy of Parkinson's disease, by administration of the 2 missing regulatory hormones: Valentonine and 6-Methoxy-Harmalan**, by transdermal route, in the form of a **mixed patch, applied at bedtime and removed in the morning upon waking**. These patches will deliver, into the bloodstream, overnight, over a period of approximately 8 hours, quantities of VLT and 6-MH capable of increasing the functioning of the surviving dopaminergic neurons, therefore variable according to the importance destruction of dopaminergic neurons and pineal secretion in patients. This, under the same conditions as their physiological secretion by the pineal gland during nighttime.

3- The treatment of Parkinson's disease with L- dopa and dopamine agonists is deleterious and totally irrational

3-1- First of all, it should be remembered that **L-dopa** (L-dihydroxy-phenyl-alanine) is an amino acid biosynthesized from Tyrosine (para hydroxy-phenylalanine), **not only in dopaminergic neurons**, where **it is the precursor of dopamine**, but also **in noradrenergic neurons**, where **it is the precursor of noradrenaline** (see Figure 11, and Appendix I).

Figure 11

L-dopa is the precursor of dopamine in dopaminergic neurons, and noradrenaline in noradrenergic neurons



Under these conditions, the administration of L- dopa will increase, in the same proportions, both **the dopamine concentrations** in the synaptic clefts of the dopaminergic neurons, and **the noradrenaline concentrations** in the synaptic clefts of the noradrenergic neurons (see **Appendix I**). **In the same way as for all dopaminergic receptors, there follows a considerable number of undesirable effects due to the activation of all the α_2 noradrenergic receptors of the organism.** Thus, among other undesirable effects, the increase in noradrenaline, which follows the administration of L-dopa, in the synaptic slots of the α_2 noradrenergic receptors, will cause a drop in blood pressure. This is the reason why vasopressive drugs need to be administered to many patients, treated with L-dopa, and victims of orthostatic hypotension. To correct these manifestations, Midodrine (Gutron^{R}), a vasopressor, antihypotensive drug, is most often used.

3-2- The uselessness of L-dopa decarboxylase inhibitors should be emphasized

One may wonder what is the usefulness of the inhibitors of L-dopa-decarboxylase, (Benserazide, Carbidopa), systematically used in combination with L-dopa (Modopar^{R}, Sinemet^{R}, Stalevo^{R}), since this enzyme, capable of decarboxylating all amino acids, without specificity, is only present in dopaminergic, noradrenergic (see Figure 10), and serotoninergic neurons, as well as in the pineal gland; but absent from the circulating blood and everywhere

else in the body. It is essential for the biosynthesis of dopamine (in dopaminergic neurons) and noradrenaline (in noradrenergic neurons), starting from L-Tyrosine, as well as for the biosynthesis of serotonin in serotonergic neurons and in the pineal gland from L-Tryptophan.

This enzyme is capable of decarboxylating all amino acids. If, as the pharmaceutical companies using these L-dopa-decarboxylase inhibitors claim, this enzyme was present in the bloodstream, we could no longer eat, since all the amino acids, which come from proteins in our diet, and which used to build us, according to the genetic code, would be destroyed.

L-dopa is present in Mucuna Pruriens, and **Mucuna capsules which contain 100 mg of L-dopa have the same activity, in the treatment of Parkinson's disease, as Modopar^{R} which contains 100 mg of L-dopa and 25 mg of Benzerazide**. **Same thing for Sinemet^{R} and Stalevo^{R} with Carbidopa**. In reality these inhibitors have been introduced into these 3 antiparkinsonian drugs, by pharmaceutical laboratories, because they have enabled them to take out intellectual property patents, and to increase the prices of their drugs, compared to extracts of Mucuna Pruriens, including they couldn't have a monopoly. In addition, the toxicity specific to these unnecessary inhibitors is added to the toxicity of L-dopa, so that the extracts of Mucuna Pruriens are more active and less toxic than Modopar^{R}, Sinemet^{R} or Stalevo^{R}. And we are extremely surprised to find that the extracts of Mucuna Pruriens which contain L-dopa, are classified in the category of food supplements, over the counter outside pharmacies.

3-3- Finally, the fact of administering L-dopa and dopaminergic agonists, during the 24 hours of the biological cycle, leads to a continuous activation of the dopaminergic receptors of the striated gray nuclei and of the black substance, with muscle relaxation permanent. This dosing regimen goes against the true therapeutic objective, which consists in causing muscle relaxation when the organism is in sleep mode, and, conversely, muscle contraction when it is in wake up mode.

4- Treatment of Parkinson's disease with mixed patches

With mixed transdermal patches, the concomitant administration of VLT and 6-MH is added to the endogenous secretion of VLT and 6-MH, which makes it possible to increase the functioning of the surviving neurons, and to compensate for the loss of the D_1 dopaminergic neurons.

From now on, Parkinson's disease will be treated by application of a mixed patch (VLT + 6-MH), which will make it possible to deliver to the organism, during the period of application, identical doses of VLT and 6-MH, between 10 and 160 micrograms. The doses administered must be sufficient to allow the surviving neurons to compensate for the incapacity of the destroyed neurons, whatever the neuronal destruction and the secretion of the 2 pineal hormones.

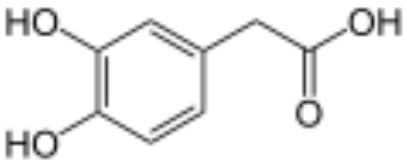
However, this treatment will only be fully effective after complete withdrawal from L-dopa and other dopamine agonists who oppose the therapeutic action of VLT and 6-MH.

Appendix I

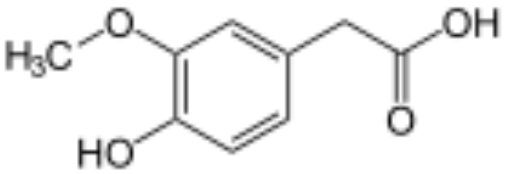
Administration of L-dopa causes a dramatic increase in the release of dopamine and noradrenaline at the place of dopaminergic receptors and noradrenergic receptors, respectively.

The dosages of the 3 neurotransmitters, dopamine, noradrenaline and serotonin were carried out in a patient suffering from Parkinson's disease and treated with Sinemet LP (100 mg of levodopa / 25 mg of carbidopa) at a rate of 3 tablets per day (morning, noon, and evening).
As these neurotransmitters do not exist in the blood since, as soon as they are released at the synaptic spaces of the corresponding neurons, and after stimulation of the receptors located on the post synaptic side of the neurons, they are:
- either recaptured by the presynaptic neuron;
- or instantly metabolized, in particular undergoing oxidative deamination under the action of the enzymes mono-amine oxidases (M.A.O.).
Under these conditions, only the metabolites of these 3 neurotransmitters can be measured, the quantities of which are excreted in the urine, using HPLC assay method. Thus, we measure the rates of their urinary metabolites:

- 3,4 dopac (3,4-dihydroxy-phenylacetic acid) and **HVA** (Homo Vanillic Acid), which are **dopamine metabolites**, the quantities of which are excreted in the urine, indirectly account for the quantity of dopamine released in the synaptic spaces of all D_1, D_2, D_3, D_4, D_5 dopaminergic receptors in the body.

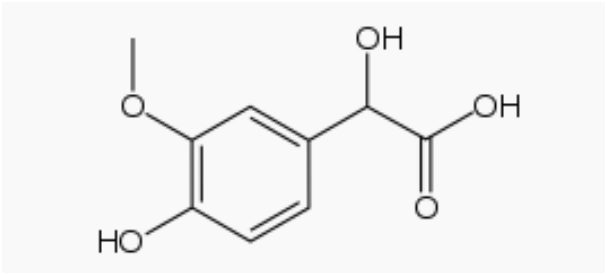


3,4-Dihydroxyphenyl-acetic acid (DOPAC)



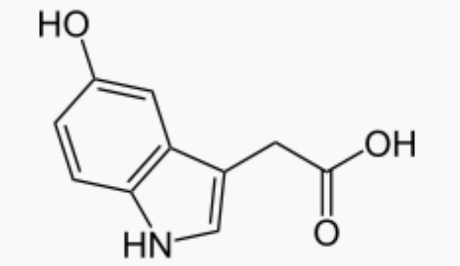
Homovanillic acid (HVA)

- **VMA** (Vanyl Mandelic Acid: *(R, S) 2-hydroxy-2- (4-hydroxy-3-methoxyphenyl) acetic acid)*), vanillyl-mandelic acid, **metabolite of noradrenaline**, the quantities of which are excreted in the urine, give an indirect account of the quantity of noradrenaline released in the synaptic spaces of all the α_1, α_2, β_1, β_2, β_3 noradrenergic receptors of the organism.



Vanillyl Mandelic Acid (VMA)

- **5-HIAA** (5-hydroxy-indolacetic acid), **a metabolite of serotonin** (5-HT: 5-Hydroxy-Tryptamine), the quantities of which are excreted in the urine, indirectly account for the quantity of serotonin released in the synaptic spaces of all the body's serotonergic receptors. Among these, the best known are the serotonergic receptors 5-HT_1 (sous types 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), 5-HT_2 (sous types 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_6 et 5-HT_7.



5-Hydroxy-Indol-Acetic-Acid (5-HIAA)

This biological assay is usually of limited interest, as it reports only on the amounts of neurotransmitters released at the places of all dopaminergic, noradrenergic and serotonergic receptors in the body. It is therefore difficult to draw conclusions, by linking quantitative variations in the urinary excretion of their metabolites to neurological dysfunctions. But, in this case, the **considerable increases in urinary excretion of the metabolites of dopamine and noradrenaline, multiplied by 5, for noradrenaline** (**109,57 μg/g of creatinine**, while the scale of excretions normal is between 15.70 and 34.30 μg/g of creatinine) and **multiplied by 10 for dopamine** (**1 783,24 μg/g of creatinine**, while the scale of normal excretions is between 116, 20 and 230 μg/g of creatinine). **These results** (see Figure 12) **clearly show that the administration of L-dopa simultaneously causes significant increases in dopamine and noradrenaline, at the places of their respective receptors**, which is normal since L-dopa is the precursor of these 2 neurotransmitters in dopaminergic and noradrenergic neurons (see Figure 11). On the other hand, the release of serotonin at the receptor level is not modified, which is logical since the precursor of serotonin, in the serotonergic neurons, and the pineal gland, is not L-dopa, but 5- hydroxy-tryptophan.

Figure 12

Assessments of the amount of dopamine, noradrenaline and serotonin released at the places of their receptors, based on measurements of urinary excretion of their metabolites.

(Results reproduced with the authorization of Mrs. Fernande M., suffering from Parkinson's disease, and treated with L-dopa)

NEUROTRANSMETTEURS
Dosage par HPLC

	Results		Normal values
CREATININE URINAIRE	0,158	g/l	
DOPAMINE	**1 783.24**	µg/g.creat	(116,20–230,00)
3,4 DOPAC (Acide dihydroxyphénylacétique)	2,32	mg/g.créat	(0,70–4,00)
HVA	**34,70**	mg/g.créat	(2,43–5,20)
NORADRENALINE	**109,57**	µg/g.créat	(15,70–34,30)
VMA (Acide Vanillylmandélique)	2,84	mg/g.créat	(2,10–3,85)
ADRENALINE	3,27	µg/g.créat	(1,27–6,10)
SEROTONINE	95,11	µg/g.créat	(61,50–116,80)
5 HIAA (Acide 5 OH indolacétique)	**1,27**	mg/g.créat	(2,03–4,06)