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FUNCTION AND MECHANISM OF ACTION OF ALPHA-METHYLDOPA: AN UPDATE

R.G. Bellomo*

Faculty of Physical Education Sciences, University "Carlo Bo", Urbino, Italy.

Correspondence to:
Rosa G. Bellomo,
Faculty of Physical Education Sciences,
University "Carlo Bo",
61029 Urbino, Italy.
e-mail: rosa.bellomo@uniurb.it

ABSTRACT

Methyldopa is a central α-2-adrenergic receptor agonist capable of reducing blood pressure by relaxing and dilating the vessels. α-methyldopa allows blood to flow faster and for its sufficent supply to the tissues. At the level of the sympathetic nervous system, the metabolization of α-methyldopa by neurons leads to the formation of methylated norepinephrine, which is less active than norepinephrine on nerve impulses. The nerve impulses allow the release of the "false neurotransmitter", α-methyl norepinephrine, which exerts a weaker response than the peripheral effector, an effect which is also exerted on the blood vessels. Direct stimulation with α-methyldopa produces an active, or in some cases, slightly reduced response of the post-ganglionic sympathetic system, and so methyldopa does not block the response to direct stimulation of the postganglionic sympathetic system in the vessels. In experimental animals, methyldopa has been seen to suppress vascular resistance and reduce blood pressure without affecting post-ganglionic sympathetic activity. In some neurodegenerative diseases, such as Parkinson's disease (PD), there is a reduction in dopamine which leads to reduced mitochondrial respiratory activity and lower alpha-ketoglutarate dehydrogenase activity.

KEYWORDS: *alpha-methyldopa, neurotransmitter, L-Dopa, CNS, Parkinson's disease, neurodegeneration*

INTRODUCTION

α-methyldopa, a methylated analogue of L-Dopa, is part of the biosynthetic pathway that leads to the synthesis of norepinephrine under physiological conditions (1). Part of the α-methyldopa is converted into α-methyl dopamine by the action of the Dopa-decarboxylase enzyme, which in turn is transformed into α-methyl norepinephrine by the β-hydroxylating enzyme (2). The antihypertensive effect of α-methyldopa is characterized by a marked decrease in peripheral vascular resistance without significant changes in cardiac output (3). This effect is accompanied by a selective reduction in renal circulation resistance with a consequent increase in glomerular flow (4). The mechanism through which α-methyldopa determines these hemodynamic effects is not yet clear and is still the subject of numerous studies and experimental investigations. From a biochemical point of view, the pharmacological action of methyldopa is different than other antihypertensive drugs and simple to understand (5). In fact, the exact correlation between the observed pharmacological effects and the biochemical events induced by this simple analogue in metabolism leading to the biosynthesis of the adrenergic neurotransmitter is not yet completely established (6).

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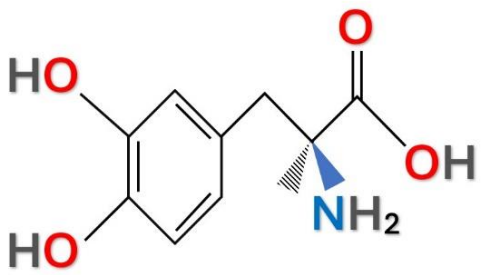

Fig. 1. *Chemical structure of α-methyldopa, a methylated analogue of L-Dopa.*

DISCUSSION

In the sympathetic neuron, the metabolic use of α-methyldopa, a natural precursor L-dopa, leads to the formation of methylated norepinephrine which proves to be substantially less active than norepinephrine regarding the transmission of nerve impulses at the sympathetic level (7). For this reason, α-methyl norepinephrine is referred to as a "false neurotransmitter" (8). One of the main mechanisms of action of methyldopa is the formation of α-methyl norepinephrine, which replaces the real neurotransmitter in the deposits located at the sympathetic nerve endings (9). Upon the arrival of nerve impulses, the release of the "false neurotransmitter" results in a much milder response of the peripheral effector, i.e., with a reduction in vascular tone and the vasoconstrictor response (10). In fact, the administration of α-methyldopa in experimental animals results in a depletion of tissue deposits of norepinephrine and the appearance of methyl norepinephrine. However, the formation of the "false transmitter" and the consequent reduction of peripheral sympathetic activity does not yet fully account for the pharmacological effects induced by α-methyldopa (11).

In animals treated with α-methyldopa, the response to direct stimulation of the post-ganglia sympathetic system does not appear blocked, but only partially reduced in some cases, and even normal in others (12). Thus, methyldopa, even in large doses, does not block the response to direct stimulation of the postganglionic sympathetic system in the heart and in peripheral vascular resistance (13). For example, in dogs, it has been demonstrated that methyldopa decreases the vascular resistance of the innervated limbs without causing an appreciable decrease in post-ganglionic sympathetic activity (1).

Numerous clinical studies have also confirmed that methyldopa reduces blood pressure in humans, both in an upright or supine position (3). In these cases, the simple inhibition of the peripheral sympathetic nervous system does not seem to be sufficient to explain the mechanism of action of methyldopa. It therefore seems logical to think that other factors intervene in determining the pharmacological response to the substance. Worthy of particular interest is the hypothesis that reduced adrenergic activity in the central nervous system (CNS) is also responsible, at least in part, for the effects of methyldopa (14).

Today, the formation of methyl norepinephrine from methyldopa in the adrenergic centers of the CNS is known. It is hypothesized that the hypotensive action of methyldopa is partly due to the formation of methyl norepinephrine in the brain, which replaces the much more potent natural neurotransmitter (15). Consequently, there is a notable decrease in sympathetic activity of central origin, which in turn is responsible for the fall in peripheral vascular resistance (16). The administration of a potent peripheral inhibitor of the Dopa-decarboxylase enzyme does not prevent the hypotensive action of methyldopa. In other words, when the formation of methyl norepinephrine ("false neurotransmitter") is blocked in the peripheral sympathetic, but not in the central adrenergic pathways, a drop in peripheral vascular resistance still occurs (17). A plausible explanation for this fact is that the formation of the "false neurotransmitter" in the CNS results in a substantial reduction in the activity of the adrenergic centers, which in turn are responsible for peripheral vascular responses (18).

This is supported by various clinical studies and experimental research. For example, in experimental animals, the infusion of methyldopa into the vertebral artery reduces systemic arterial pressure (19). The same dose injected intravenously into the peripheral circulation does not significantly change blood pressure values (20). The hypotensive effect of small doses of methyldopa injected into the vertebral artery is abolished by pre-treatment with an inhibitor of the Dopa-decarboxylase enzyme that can cross the blood-brain barrier (BBB) (19). However, if an inhibitor that does not cross the BBB is used, the action of methyldopa is not blocked. From these data it seems suggestive to conclude that an important part of the mechanism of action of the drug is carried out through a decrease in central adrenergic activity and

that this decrease occurs mostly due to the increase of methyldopa in the biosynthetic chain of norepinephrine, leading to the formation of a "false neurotransmitter" such as α-methyl norepinephrine (21).

Like other antidepressant drugs, α-methyldopa has been the subject of numerous studies from which an important observation emerged, which in a certain sense, characterizes and distinguishes this drug from the others. While it has been observed that treatment with reserpine, chlorothiazide, and hydralazine generally induces an increase in renin activity in the plasma, α-methyldopa substantially reduces renin levels both in laboratory animals and in hypertensive subjects (22). In dogs, intravenous administration of α-methyldopa for 7 and 10 days causes a decrease in plasma renin activity (from 13 μg/ml to 7 μg/ml) of the produced angiotensin II (23). Again, in dogs, α-methyldopa blocks the increase in renin produced by sympathetic stimulation of the kidney without preventing the vasoconstrictor effect induced by the stimulation itself (24). Also in this case, the effect of α-methyldopa does not seem to be attributable to a generic depression or blockade of adrenergic activity, but rather either to a specific effect of the drug at the sympathetic neurological level or to an effect on the CNS (25).

In this regard, it is interesting to observe that the "false neurotransmitter" α-methyl norepinephrine synthesized by the neuron from α-methyldopa is much less active than norepinephrine in stimulating renin secretion (26). In some experiments, it has been seen that the infusion of norepinephrine in dogs induces a clear increase in plasma renin, while the infusion of equivalent doses of α-methyl epinephrine is followed by a slighter increase in renin (27). The depressant action of α-methyldopa on the renin system does not seem to be mediated by modification of the electrolyte balance or by the secretion of aldosterone (28). These parameters are not modified in hypertensive subjects after administration of the drug. Even in the clinic, it has been confirmed that α-methyldopa substantially decreases renin activity both in normotensive subjects and in non-severely hypertensive patients with renal failure (29).

From all these observations, another important characteristic of α-methyldopa emerges which certainly deserves serious consideration in the analysis of the drug's mechanism of action. It is still unclear whether the suppression of renin activity is mediated exclusively by the action of α-methyldopa on the post-ganglionic sympathetic system, or whether it is also mediated by the action of the drug on the central adrenergic pathways (30).

α-Methyldopa and Parkinson's Disease

In 1817, James Parkinson first described Parkinson's disease (PD) as a disease characterized by a drastic decrease in dopamine. This neurodegenerative disease is the most widespread after Alzheimer's disease. PD is an extrapyramidal syndrome characterized by muscle rigidity that manifests with resistance to passive movements (31). Patients affected by this neurological disorder mainly present diffuse tremors and muscle hypertonicity. The tremors usually affect the muscles of the limbs and head. In the hands, the continuous movements of the thumb and forefinger resemble pilling or rolling movements. The patient has difficulty moving and tends to fixate on their facial expression, an effect called Parkinsonian mask (32). Tremor can also occur during a state of rest and can increase in cases of anxiety and bradykinesia, causing difficulty in starting and finishing movements. The course and symptoms of PD worsen over time, even though treatment with new drugs and non-pharmacological therapies have significantly improved patients' quality of life.

At an anatomopathological level, the disease presents progressive and prolonged neuronal degeneration of the "substantia nigra pars compacta" (33). In PD patients, the quantity of dopamine is significantly reduced, as is the concentration of neuromelanin with a consequent decrease in pigmentation (34). In addition, patients also present reduced mitochondrial respiratory activity and lower alpha-ketoglutarate dehydrogenase activity (35).

CONCLUSIONS

α-methyldopa is characterized by an antihypertensive effect and a marked decrease in peripheral vascular resistance without significant changes in cardiac output. Drastic decrease of dopamine characterizes PD which is a neurological disorder which presents muscle rigidity with resistance to passive movements. The therapies available today for PD involve dopamine replacement and other pharmacological treatments and help to prolong lifespan but are not sufficient to block the development of this disorder. Because the causes of the disease are not yet known, future studies should focus on this topic to develop therapies and improve prevention (34). In addition, the future goal of research should be to distinguish growth factors that can replace degenerated gray matter.

Conflict of interest

The author declares that they have no conflict of interest.

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