

Ephedrine: direct, indirect or mixed acting sympathomimetic?**Paresh Solanki, Preeti P. Yadav*, Naresh D. Kantharia**

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ABSTRACT

Ephedrine is the principal alkaloid that is responsible for the physiological effects of herb ephedra. This herb is found in literature of India and China since ancient times because of its effectiveness as an anti-asthmatic. Ephedrine is classified as sympathomimetic drug. Despite extensive work in this field, the mechanism of action of ephedrine remains controversial. Initial studies classified ephedrine as indirectly acting sympathomimetic, subsequent studies showed ephedrine acts by mixed action by releasing noradrenaline and by acting directly on receptors. However, few recent studies on rat have shown predominant direct action on adrenergic receptors. Hence, there is marked controversy existing whether ephedrine is directly, indirectly or mixed acting drug.

Keywords: Ephedrine, Sympathomimetic**INTRODUCTION**

Ephedrine, present in *ma-huang*, is the principal alkaloid responsible for the physiological effects of this herb. Ephedra refers to the dried stem ephedra species.¹ *Ma huang* (*Ephedra vulgaris* var. *Helvetica*, family *Gnetaceae*) has been known in Chinese medicine for some 5000 years. The plant is indigenously grown in India, Pakistan, and China. The ephedra has historically been used by Asian cultures for its effectiveness as an anti-asthmatic and central nervous system (CNS) stimulant, as well as for its ability to induce an intoxicated state.² Ephedrine was initially isolated and identified as the primary active alkaloid responsible for the effects of ephedra by Chen and Schmidt in 1924. Ephedrine causes an increase in systemic arterial pressure, heart rate, and cardiac output. However, the mechanism of the pressure response to ephedrine is uncertain. Initial studies classified ephedrine as indirectly acting sympathomimetic, subsequent studies showed ephedrine acts by mixed action by releasing noradrenaline and by acting directly on receptors. However, few recent studies on rat have shown predominant direct action on adrenergic receptors. Hence, there is marked

controversy existing whether ephedrine is directly, indirectly or mixed acting drug.

HISTORY

Ephedra (*ma-huang*) is a Chinese shrub that had been known for at least 5000 years. The Chinese emperor ShenNung, around 2700 BC, cataloged 365 herbs in terms of their bitterness, the main groups being strong, medium, and mild. Ma-huang, whose literal translation means "*hemp yellow*", was placed in the medium group. Professor Nagayoshi Nagai, the Japanese chemist discovered and isolated ephedrine for the first time in 1885.³ In 1886, the German Chemical Company E Merck obtained the pure compound ephedrine.⁴

Ephedrine was forgotten then after it was rediscovered by Chen and Schmidt in the early 1920s. The principal reason for this ignorance was that the original papers from Nagai (and Merck) had been published either in Japanese or German, which had limited proficiency. When KoKuei Chen and Carl F Schmidt took up their posts in 1920 as lecturers at the

Peking Union Medical College they decided to investigate promising drugs from the Chinese pharmacopoeia.⁵ The American pharmacologist Professor Raymond Ahlquist (1914-1983), studied the actions of ephedrine and led to an important discovery on the classification of adrenergic receptors into the alpha and beta types, which was a defining moment in the history of autonomic pharmacology.⁶ Gradually, ephedrine became a highly popular and effective treatment for asthma, particularly because, unlike adrenaline (standard therapy at that time), it can be given by mouth. Ephedrine as a treatment for asthma reached its zenith in the late 1950s.

OFFLINE USES OF EPHEDRINE

During early 19's ephedrine was investigated by various scientists. Many kind of different therapeutic uses emerged from research about ephedrine. Ephedrine was used for asthma, hay fever, bronchitis and emphysema, whooping cough, spinal anesthesia, hypotension, shock, Adams-Stoke's syndrome, as a nasal decongestant, as an antidote for narcotic drugs, urticaria, dermatitis medicamentosa, leprosy, dysmenorrhea, as psychostimulant, as a remedy for the weight loss, etc.⁷⁻¹⁰ Since 1950s, there has been a gradual and inevitable decline in its therapeutic use. From mainstream medicine, ephedrine moved into the twilight zone of street drugs and nutritional supplements. Ephedra and ephedrine products are now banned in many countries, as they are a major source for the production of the addictive compound methamphetamine (crystal meth).²

CURRENT USES OF EPHEDRINE

Currently, ephedrine is being used to increase blood pressure in patients with decreased peripheral resistance in conditions such as spinal anesthesia, especially during caesarean section or intoxication with antihypertensive medications. In many countries, it is still widely available as an over-the-counter medication or as herbal medications. Such kinds of preparations containing ephedrine are commonly available for cough, asthma, and bronchitis. Ephedrine alkaloids are also found in different herbal tonics available in the market for different uses. Use of these herbal medicines has been linked to cardio toxicity in humans.¹¹⁻¹⁷

CHEMICAL STRUCTURE OF EPHEDRINE AND RELATED COMPOUNDS

Structurally ephedrine is a β -phenylethylamine, consisting of a benzene ring and an ethylamine side chain (Figure 1). Structure is similar to catecholamines such as noradrenaline, adrenaline, and dopamine. These catecholamines have hydroxyl groups substituted at positions 3 and 4 of the benzene ring, which are absent in non-catecholamines like ephedrine. These substitutions lead to increase in activity at α and β receptors, but also made them susceptible for metabolism by catechol-O-methyl-transferase. Phenylethylamine backbone

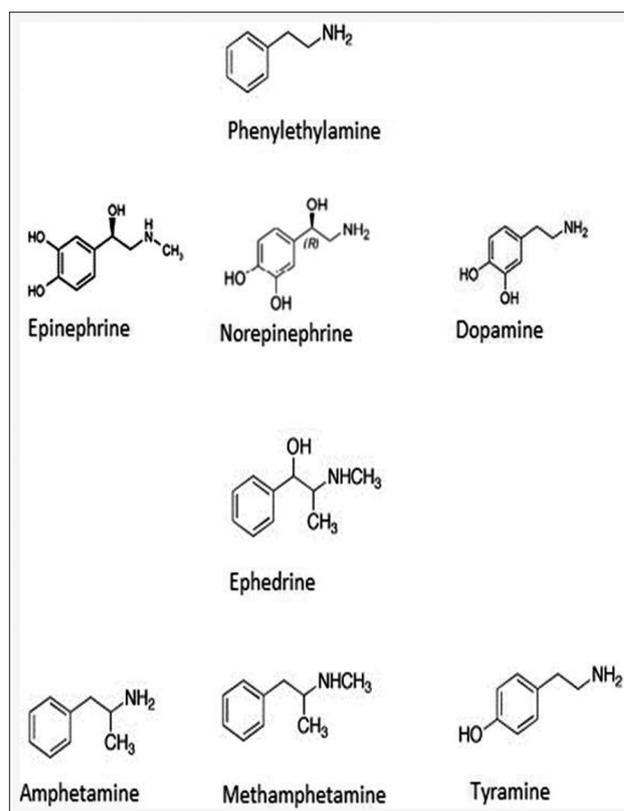


Figure 1: Chemical structures of ephedrine and related compounds.

is as well present in amphetamine, methamphetamine, and tyramine. Substitution at α -carbon atom of ephedrine, amphetamine, and methamphetamine prevents oxidation by monoamine oxidase, making them longer acting agents. Methyl substituent on amino group in amphetamine produces methamphetamine. Substitution of a hydroxyl group on the β -carbon of methamphetamine produces ephedrine with lower lipid solubility and fewer CNS actions. Ephedrine is also known as the β -hydroxy analog of methamphetamine. However, such substitution greatly enhances agonist activity at both α and β adrenergic receptors. (Figure 1).¹⁸ Although ephedrine is less potent than methamphetamine as a central stimulant, it has greater activity for α and β receptors. Levorotatory substitution on β carbon of l-ephedrine has more peripheral activity on α and β receptors compared to d-ephedrine (pseudoephedrine), which has dextrorotatory substitution on β carbon.¹⁸

RECEPTORS FOR EPHEDRINE

Like adrenaline and noradrenaline, ephedrine is also a sympathomimetic drug. Ahlquist showed that the sympathomimetic effects of adrenaline and noradrenaline on different systems are mediated by stimulation of α and β adrenergic receptor subtypes. Adrenaline and noradrenaline increase systemic arterial blood pressure, increase peripheral vascular resistance, increase heart rate, increase force of contraction of heart and modulate the blood flow to various vascular beds by their interaction with

α and β adrenergic receptors. Sympathomimetic drugs act on these receptor subtypes of target tissues with variable affinity and produce their effects. Ephedrine, tyramine, amphetamine, and other related substances also produce actions mimicking sympathetic stimulation. Hence, they are also sympathomimetic drugs. The prominent effects of ephedrine are similar to stimulation of the sympathetic nervous system in “fight and flight” response. Effects of ephedrine are essentially the same in isolated organs or after the destruction of the CNS, indicating that ephedrine acts peripherally like adrenaline and is a true “sympathomimetic amine.” Intravenous injection or oral ingestion of ephedrine causes rise in blood pressure, which lasts for longer duration than adrenaline. Simultaneous vasoconstriction (α_1) and cardiac stimulation (β_1) produced by ephedrine are responsible for the rise in blood pressure.^{9,19} In addition, at toxic doses ephedrine depresses heart. Stimulation of α adrenergic receptor is responsible for an increase in arterial pressure, and peripheral resistance, whereas β_1 adrenergic receptor stimulation is responsible for an increase in heart rate and increase in force of contraction. Ephedrine causes relaxation of bronchial and intestinal smooth muscle mimicking adrenaline. Respiratory and intestinal smooth muscle relaxations are mediated by stimulation of β_2 receptors by ephedrine.^{20,21}

CLASSIFICATION OF SYMPATHOMIMETIC AMINES

According to standard text books of pharmacology sympathomimetic drugs have been classified into three groups: direct acting, indirect acting and mixed acting (Figure 2). Adrenaline, noradrenaline, isoprenaline, etc. are directly acting drugs; they act as an agonist for α and β adrenergic receptor subtypes. Amphetamine, methamphetamine, tyramine, and related compounds are classified as indirectly acting sympathomimetic. It is believed that indirectly acting sympathomimetic agents have little or no agonistic action on adrenergic receptors. However, indirectly acting sympathomimetic agents have an ability to stimulate the release of endogenous catecholamine from adrenergic nerve terminals and adrenal medulla and this endogenous catecholamine, noradrenaline has agonistic action on adrenergic receptors (Figure 2). The mechanisms by which these drugs release noradrenaline from nerve endings are complex. All such agents are substrates for norepinephrine (NE) transporter. As a result of their transport across the neuronal membrane and release into the axoplasm, they make the carrier available at the inner surface of the membrane for the outward transport of noradrenaline (“facilitated exchange diffusion”). In addition, these amines are also capable of mobilizing noradrenaline stored in the vesicles by competing with catecholamines for the vesicular uptake process, thereby, indirectly activating adrenergic receptors to induce cardiovascular changes. Structurally ephedrine is related to indirectly acting sympathomimetic agents like amphetamine and methamphetamine, but the mechanism

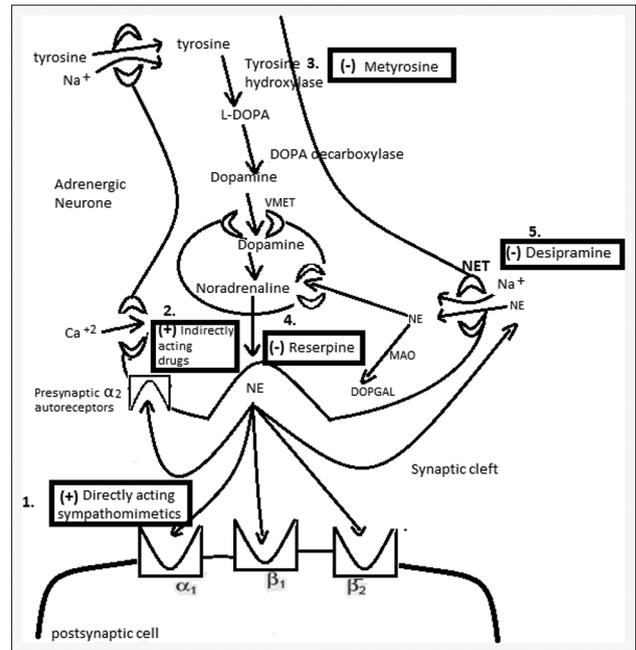


Figure 2: Mechanism of action of sympathomimetic agents. (1) Directly acting sympathomimetics like adrenaline noradrenaline, isoprenaline act directly on adrenergic receptors. (2) Indirectly acting drugs like tyramine, amphetamine, methamphetamine, etc. act by releasing noradrenaline from presynaptic adrenergic nerve terminal. (3) Metyrosine inhibits tyrosine hydroxylase enzyme and inhibits noradrenaline synthesis. (4) Reserpine inhibits vesicular mono amine transporter (VMAT) and decreases vesicular uptake of noradrenaline. (5) Desipramine inhibits norepinephrine transporter (NET) and blocks axonal uptake of noradrenaline.

of action of ephedrine remains unsolved. Initially, it was classified as indirectly acting sympathomimetic agent.²²⁻²⁶ Further studies exploring the mechanism of action of ephedrine showed some direct action on α and β adrenergic receptors.^{21,27-30} Currently, ephedrine is considered as a mixed acting sympathomimetic agent having very weak direct action and the majority of its actions are through release of noradrenaline from adrenergic nerve terminals and from the adrenal medulla.

Studies showing indirect or mixed mechanism of action of ephedrine

In late 1920s, because of superiority of ephedrine over adrenaline in the treatment of asthma, various scientists directed to explore further actions and mechanism of action of ephedrine. First attempt was made by Burn and Tainter in 1931; they studied the effect of cocaine on responses of sympathomimetic drugs. In the results, they found that actions of adrenaline are increased, and that of tyramine and ephedrine are diminished or abolished by cocaine, both on the heart in the heart-lung preparation, and on the vessels of the hind limbs perfused by the Dale-Schuster pump. Tyramine

and ephedrine had no action on the denervated pupil, though to adrenaline it was supersensitive.³¹ In 1932, Burn recorded that denervation of the cat's foreleg by removal of the stellate ganglion led to loss of the vasoconstrictor actions of tyramine and ephedrine. But there was no effect on action of adrenaline. Tyramine and ephedrine did not dilate the isolated iris of the cat's eye if the post-ganglionic sympathetic fibers have been degenerated.^{32,33}

Fleckenstein and Burn (1953) studied the effect of sympathomimetic amines on nictitating membrane of cat and showed direct and indirect actions of ephedrine.²⁵

The indirect mechanism of action was also proved in the reserpine-treated animals by Burn and Rand (1958). Tyramine, ephedrine and amphetamine lose their pressure actions in the spinal cat and no longer cause contraction of the nictitating membrane or of the splenic volume. They also lose their constrictor actions in the perfused dog's hind leg.²³

In the study by Trendelenburg and Fleming (1960), reserpine pretreatment showed a decrease in sensitivity of the nictitating membrane to ephedrine, but increase in the dose of ephedrine produced nearly same maximal responses as in nictitating membrane without reserpine pretreatment. These finding suggested that in addition to indirect action, ephedrine also have a direct action on the nictitating membrane.³⁴

In one comparative study on the innervated and on the chronic sympathetic-denervated cat's iris, the mydriatic action of ephedrine was reduced after iris denervation, suggesting that normally ephedrine acts partly by the release of a dilator substance in the iris. The dilator effect could be elicited when tyramine had either no effect, or a biphasic or a miotic action. This showed ephedrine has also a direct adrenaline-like action on the iris.²⁶

In another study of Cairoli et al. (1961) reserpine pretreatment decreases the maximum contractile response of isolated papillary muscle to ephedrine, explaining that a direct action was not largely responsible for the residual effect of ephedrine.²⁴ De Moraes et al. (1968) also demonstrated the indirect mechanism of action of ephedrine in forelimb and coronary vasoconstriction.³⁵

Chidsey et al. found that intravenous injections of tyramine, amphetamine and ephedrine resulted in the release of noradrenaline from the heart into the coronary sinus of the intact anesthetized dog.³⁶

Therefore, above studies indicate that ephedrine induced contraction of the nictitating membrane, constriction of the pupil; forelimb vasoconstriction and coronary vasoconstriction are mediated by an indirect mechanism.

In a comparative study by Andersen et al. (1964) mephentermine and ephedrine were compared for

cardiovascular effects in man and showed that stimulant actions of ephedrine result from direct and indirect activation of α and β adrenoceptors.³⁷

Cohn et al. (1965) studied the systemic hemodynamic and forearm vascular effects of tyramine, ephedrine, and noradrenaline in normal male subjects and demonstrated differences in local vascular and systemic hemodynamic effects of these drugs, suggesting some inconsistency in the hypothesis that the effect of either ephedrine or tyramine is mediated exclusively by NE release.³⁸

Kobayashi et al. (2003) evaluated the sympathomimetic effects of *l*-ephedrine and *d*-pseudoephedrine on mean arterial pressure and heart rate in intact animals, sinus rate in an isolated right atrium of rat and tension development in isolated rat anococcygeal muscle and human umbilical vessels. Key results of this study showed that ephedrine has a direct action in isolated tissues and the pressure response is completely indirectly mediated *in vivo* in the rat. It has been reported that the pressure response to ephedrine is reduced following treatment with 6-hydroxydopamine, an agent which destroys adrenergic nerve terminals.²⁹ However, the regimen used in this study was not sufficient to prove indirect mechanism of action of ephedrine. It is possible that 6-hydroxydopamine causes non-specific depression of vascular responses.³⁹

Studies showing direct mechanism of action of ephedrine

In contrast to the above there are some studies, which point toward the direct mechanism of action of ephedrine on adrenergic receptor subtypes. There are few *in vitro* and *in vivo* studies, which provide evidence for direct mechanism of action of ephedrine.

Waldeck et al. (1985) measured the β adrenergic receptor mediated effects of ephedrine on the isolated tissue preparation of guinea pig tracheal rings, and found that ephedrine has relaxant effect on guinea pig trachea and this relaxant effect of ephedrine could not be reversed by pretreatment with reserpine, giving a hint that in isolated tracheal rings of guinea pigs the effect is mediated by direct activation of the adrenergic receptors on tracheal smooth muscles.²⁰

Guoyi et al. (2004) also showed direct mechanism of ephedrine alkaloids. They evaluated ephedrine alkaloids for their binding affinities on human adrenergic receptor subtypes expressed in human embryonic kidney and Chinese hamster ovary cells. Cell-based receptor gene assays were used to establish functional activity of ephedrine alkaloids at α 1A, α 2A, and α 2C adrenergic receptors.⁴⁰ Previously, Vansal and Feller (1999) also evaluated direct effects of the ephedrine isomers on human β 1, β 2, and β 3 adrenergic receptors expressed in Chinese hamster ovary cells.²¹

Direct action of ephedrine also has been demonstrated in isolated tissue preparation of guinea pig portal vein by Bao et al. (1990). The effects of ephedrine were compared with those of tyramine and phenylephrine in ring segments of guinea pig portal vein *in vitro*. Ephedrine, tyramine and phenylephrine all produced dose-dependent contractile responses, which were markedly depressed by α adrenergic receptor blocker phentolamine. Pretreatment with reserpine 1 mg/kg/day for 2 day noticeably diminished the effect of tyramine, but greatly potentiated the effects of ephedrine and phenylephrine. Both ephedrine and tyramine, but not phenylephrine, significantly increased the electric field stimulation evoked contractions of the portal veins. β -Adrenergic receptor blocker propranolol markedly inhibited this effect of ephedrine, without affecting that of tyramine. It was suggested that the effect of tyramine is mainly due to release of endogenous NE from the nerve terminals; conversely, ephedrine mainly acts on postsynaptic α adrenergic receptors directly with some noradrenaline-releasing action, which may involve the activation of presynaptic β adrenergic receptors.²⁷

In dopamine β -hydroxylase knockout (DBH $-/-$) mice the increase in systemic arterial pressure and heart rate in response to intravenous injections of ephedrine was not impaired whereas response to amphetamine was markedly reduced, when compared with responses in DBH $+/-$ mice. The pressure response to tyramine was abolished whereas pressure responses to NE, phenylephrine, dopamine, and angiotensin II were similar in DBH $-/-$ and DBH $+/-$ mice. Hence, pressure responses to ephedrine are directly mediated, whereas responses to amphetamine are dependent on the release of NE.^{30,41}

The recent study by Liles et al. (2006) showed that pressure response to ephedrine is not diminished in rats that have undetectable cardiac levels of NE and markedly attenuated response to tyramine after treatment with catecholamine depleting agents. In contrast to previous studies, which used reserpine alone, in this study combination of reserpine and metyrosine was used to deplete the presynaptic noradrenaline pool. Reserpine and metyrosine combination abolished the pressure responses of ephedrine significantly in rat; however, pressure responses of tyramine and amphetamine were not abolished by this combination. In another set of experiments they used cocaine which inhibits axonal uptake of noradrenaline; cocaine also inhibited the pressure responses of ephedrine but not of amphetamine and tyramine in rat. Hence, this study also indicates predominant direct action of ephedrine on adrenergic receptors in rat blood pressure.⁴¹

SUMMARY

Ephedrine is a sympathomimetic drug. However, in spite of many studies it is not clear whether ephedrine is a directly acting or indirectly acting or mixed acting drug. Further studies are required on different species using different

regimens by different expert hands in different laboratory setups.

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