Interaction Between Dexmedetomidine and α-Adrenergic Receptors: Emphasis on Vascular Actions

Melik Seyrek, MD, PhD,* Zekai Halici, MD, PhD,*† Oguzhan Yildiz, MD, PhD,* and Hasan B. Ulusoy, MD, PhD‡

Dexmedetomidine (DEX) is a new methylol derivative with high affinity to α2-adrenergic receptors. It causes analgesia and sympatholysis, and has sedative, anxiolytic, and hypnotic effects. The use of DEX and its affinity to α2-adrenergic receptors in the body should not only be limited to sedation and anesthesia, because α2-adrenergic receptors are scattered throughout the body.

In 1948, Ahlquist et al[1] first reported α and β subtypes of adrenergic receptors that were activated by noradrenalin, the mediator of sympathetic nervous system stimulation in mammals. In light of this preliminary report, numerous studies were performed on this topic and, in 1973, α_1 and α_2 subtypes of α-adrenergic receptors were determined.[2] In subsequent investigations, gene studies were developed, and 3 subtypes, called α_{aA}, α_{1B}, and α_{1c}, for α_1-adrenergic receptors[2] and 4 subtypes, called α_{2A}, α_{2B}, α_{2C}, and α_{2D}, for α_2-adrenergic receptors were isolated.[3,4] Studies performed on isolated organ samples from several experimental animals showed that both subtypes of α-adrenergic receptors are present in postsynaptic membranes in many animal species, including rabbits and guinea pigs; α_1-adrenergic receptors are dominant.[5] In contrast, α_2-adrenergic receptors were reported to be denser only in a number of tissues, such as human saphenous vein[6] and femoral vein tissue.[7] Experimental findings show that localization of α-adrenergic receptor subtypes can differ among species and vessel segments, so the responses that occur after activation of these receptors vary.

PHYSIOLOGIC AND FUNCTIONAL DISTRIBUTION OF α_2ADRENERGIC RECEPTORS

The sympathetic nervous system plays a central role in the regulation of organ blood flow, primarily through regulating the release of epinephrine and norepinephrine, which act on α_1-, α_2-, and β_2-adrenoceptors in arteries and veins.[8] In the peripheral system, 3 α_2-adrenergic receptor subtypes have been reported to play roles in the control of the negative feedback mechanisms of neurotransmitter secretion.[9] α_2-Adrenoceptors modulate organ blood flow in a complex manner. The activation of presynaptic α_2-adrenoceptors on sympathetic nerves and in the central nervous system induces sympatholysis, whereas the activation of vascular postsynaptic receptors causes both vasoconstriction (through the activation of α_2-adrenoceptors on vascular smooth muscle cells) and vasodilatation (through the activation of α_2-adrenoceptors on endothelial cells).[8,10] This may be helpful in understanding how α_2-adrenergic receptor agonists and antagonists affect the peripheral system.[9] In the peripheral system, the activation of adrenergic receptors, which have different localizations in different species and occur in different vessel segments according to the appropriate ligands, leads to the stimulation of different signal transduction mechanisms according to the subtype of the receptor. The hypothesis that α_2-adrenergic receptors do not compose a homogenous group and may have subtypes with different pharmacologic properties first occurred by determining that the potency of prazosine required to inhibit yohimbine's linkage to the receptors is altered in different regions of human and rat brain.[11,12] In light of these findings, the regions with low affinity to prazosine were called α_{2A}, and the regions with high affinity to prazosine were called α_{2B}. It has been reported that the α_{2A} subtype of adrenergic receptors is localized in human thrombocytes, rabbit spleens, and rat submandibular glands.[13] In addition, neonatal rat lungs, rat kidney,[4] and rat atrium[14] also have been reported to have α_{2B}-subtype adrenergic receptors; it is known that the activation of α_{2B}-adrenergic receptors leads to the inhibition of adenylate cyclase enzyme and a reduction in cyclic adenosine monophosphate production.[15] Additional events, such as the activation of potassium channels, the inhibition of voltage-gated calcium channels, the activation of phospholipase C, and the activation of mitogen-activated protein kinase also have been reported.[16]

α-Adrenergic receptors, especially α_2-adrenergic receptors, can lead to several physiologic functions in relation to their localization in the body. Briefly, these functions can be summarized as the inhibition of neurotransmitter release; the regulation of blood pressure; sedation; analgesia; the regulation of insulin secretion and lipolysis; the regulation of renal function; the regulation of multiple cognitive behavioral functions; and the regulation of body temperature.[17-22] Recent studies showed that α_{2A}-receptors also can play important roles in the protection of the gastric mucosa.[23] As described earlier, the therapeutic use of both agonists and antagonists of α_2-adrenergic receptors, which are essential in the regulation of homeostasis, is

*From the *Department of Pharmacology, Gulhane Military Medical Academy, Ankara, Turkey; †Department of Pharmacology, Ataturk University, School of Medicine, Erzurum, Turkey; and ‡Department of Pharmacology, Erciyes University, School of Medicine, Kayseri, Turkey.*

Address reprint requests to Oguzhan Yildiz, MD, PhD, Department of Pharmacology, Gulhane Military Medical Academy, Ankara, Turkey. E-mail: oyildiz@gata.edu.tr

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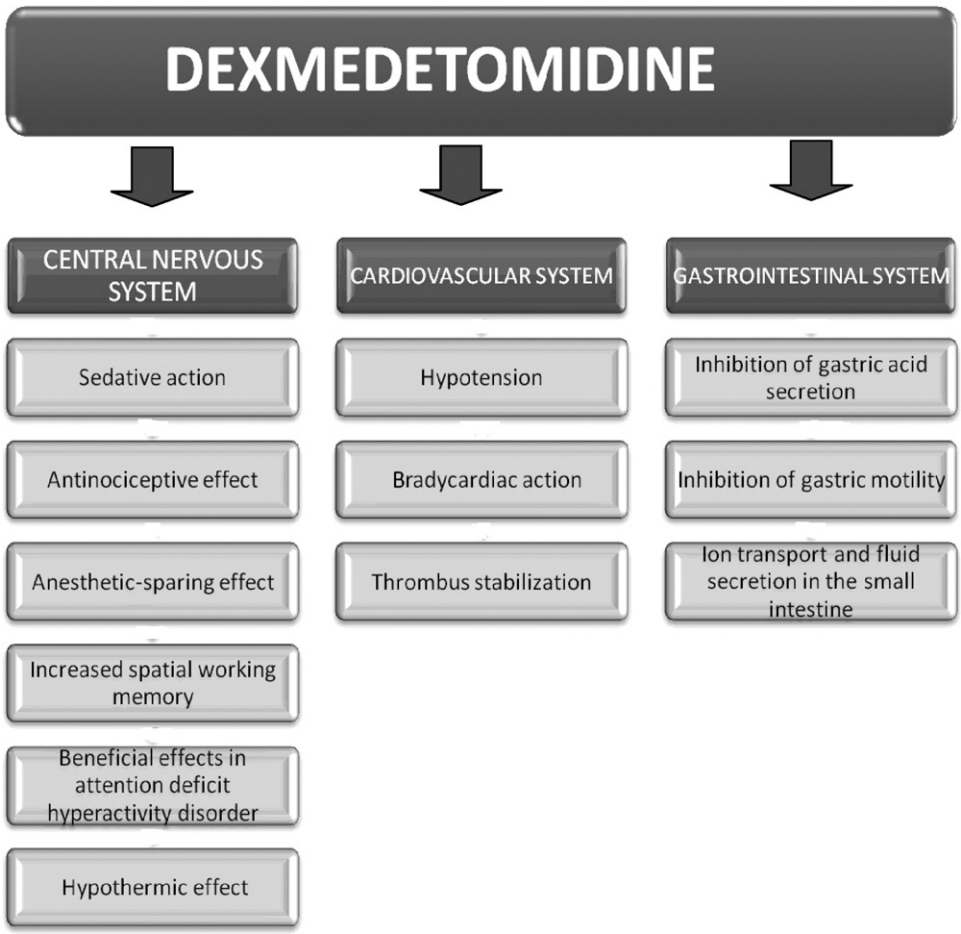

Fig 1. The effects of DEX on systems.

quite important, especially as new pharmaceutical agents and indications for these receptors still are being developed.

DEXMEDETOMIDINE: PHARMACOLOGIC PROPERTIES

In the last 30 years, norepinephrine, clonidine, DEX, brimonidine, ST-91, and moxonidine have been used as α-adrenergic agonists; DEX has attracted increased attention as an anesthetic agent because it is narcotic sparing, and so it decreases respiratory depression, prevents tachycardia and hypertension, and provides sedation while maintaining arousability and respiratory drive.[24]

DEX is a new methylol derivative with high affinity to α_2-adrenergic receptors (α_2/α_1:1,600/1).[25] Its affinities to the various subtypes of α_2-adrenergic receptors (A, B, and C) differ.[25,26] It has analgesic, sympatholytic, sedative, anxiolytic, and hypnotic effects.[27] Its antinociceptive effect also has been determined by intrathecal administration.[28] DEX is a lipophilic drug, so it can distribute rapidly within the brain-blood barrier and peripheral tissues. It is 94% protein bound, and the ratio between the concentration of whole blood and plasma is 0.66. It is metabolized in the liver and excreted through urine and feces.[29] DEX has a concentration-dependent, nonlinear pharmacokinetic profile,[30,31] which is not affected by age, weight, or renal failure.[31] Its terminal elimination half-life is 2 to 4 hours.[32] In 1999, the Food and Drug Administration allowed DEX to be used for short-term sedation of critically ill adult patients. The investigations about possible effects of DEX and, therefore, α_2-adrenergic receptors, should not be limited only to sedation and anesthesia because α_2-adrenergic receptors are scattered throughout the body, especially in tissues innervated by sympathetic afferent nerves (Fig 1). Therefore, the authors reviewed the effects of DEX on vascular structures in this article.

Certain Pharmacologic Properties Specific to DEX That Might Enable Vascular Effects

Effect on Central Presynaptic α_2-Adrenergic Receptors, Primarily Sympatholysis

α_2-Adrenoceptors are located in specific brain nuclei that regulate cardiovascular activity and are involved in modulating the sympathetic nervous system activity.[33,34] Thus, it is possible that central α_2-adrenoceptors play some role in the central control of cardiovascular functions. Shirasaka et al[35] confirmed the previous speculations that α_2-agonists induce sympatholytic effects through α_2-adrenoceptors in the central nervous system[35]; this study provided the first evidence that intracerebroventricular administration of DEX induced cardiovascular re-