Alpha-2 Agonists as Pain Therapy in Horses

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KEYWORDS

• Epidural • Constant rate infusion • Xylazine • Romifidine
• Detomidine • Medetomidine • Dexmedetomidine • Clonidine

Alpha-2 agonists, such as xylazine, clonidine, romifidine, detomidine, medetomidine, and dexmedetomidine, are potent analgesic drugs that also induce physiologic and behavioral changes, such as hypertension, bradycardia, atrioventricular block, excessive sedation and ataxia, all of which can potentially limit their systemic use as analgesics in some clinical cases. Therefore it is of utmost importance to know the individual properties of each of the alpha-2 agonists to select the ideal drug for each clinical condition, based on the duration of action of analgesia and behavioral changes.

Since the last review on this subject from this Journal,[1] the use of medetomidine and dexmetomidine has been introduced for equine anesthesia/analgesia, and although not approved in this species, their increased specificity for alpha-2 receptors may offer some potential advantages over the traditional alpha-2 agonists. Similarly, other routes of administration and benefits of alpha-2 agonists are recognized in the human and laboratory animal literature, which may prove useful in the equine patient if validated in the near future. This review presents this relevant information.

PHARMACOLOGY OF ADRENERGIC RECEPTORS

Adrenergic receptors are subdivided into alpha and beta. Both alpha and beta are further classified into alpha-1, alpha-2, beta-1, and beta-2. Alpha receptors are located postsynaptically (alpha-1 and alpha-2) and presynaptically (alpha-2) at sympathetic neuroeffector junctions of many organs (**Fig. 1**). Beta receptors are located postsynaptically and in general mediate decreased activity of the effector cells (beta-2: vasodilation, bronchodilation, uterine relaxation) or increased activity (beta-1: heart automaticity and contractility). Postsynaptic activation of alpha receptors mediate increased activity of the effector cells.

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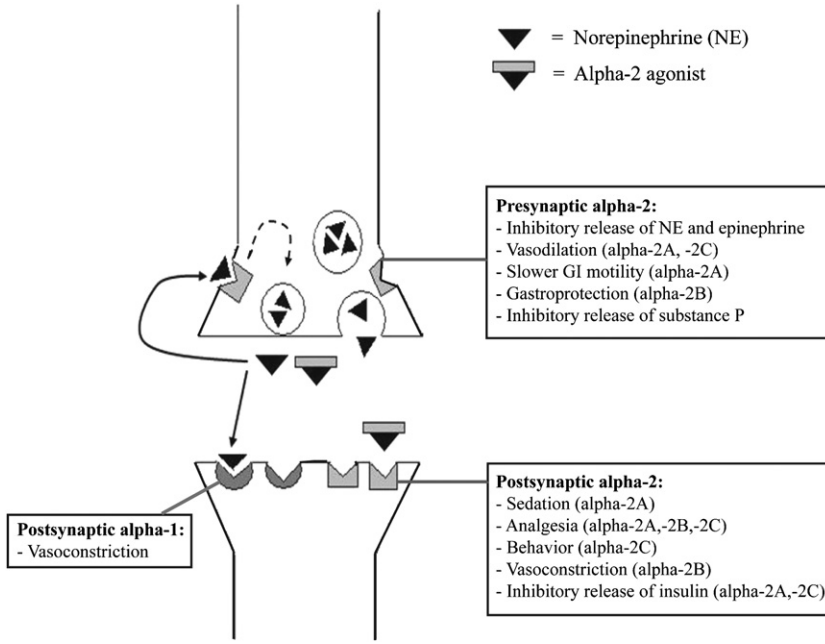

Fig. 1. Adrenergic receptors are subdivided into alpha and beta. Both alpha and beta are further classified into alpha-1, alpha-2, beta-1, and beta-2. Alpha receptors are located postsynaptically (alpha-1 and alpha-2) and presynaptically (alpha-2) at sympathetic neuroeffector junctions of many organs.

Activation of the presynaptic alpha-2 receptor inhibits the release of norepinephrine (NE) into the synaptic cleft and autoregulates its actions on the effector cells. The net effect of activation of alpha-2 adrenergic receptors is modulation of sympathetic nervous system activity by inhibition of NE. Manifestations of this response include decreased cardiac output due to decreased inotropy and decreased heart rate, as well as a reduction in systemic vascular resistance. Conversely, the activation of postsynaptic alpha receptors mediates an increase in systemic vascular resistance. Actions at centrally located alpha-2 adrenergic receptors mediate sedation, anxiolysis, analgesia, and hypnosis. It has also been shown that the alpha-1 agonistic activity can reduce the alpha-2 mediated analgesia, and it has been suggested that coadministration of an alpha-1 antagonist (prazosin) with the alpha-2 agonist may enhance analgesic potency.[2] The alpha-2/alpha-1 selectivity for alpha-2 agonists is 160 for xylazine, 220 for clonidine, 260 for detomidine, and 1620 for medetomidine or dexmedetomidine,[3] and is unknown for romifidine but higher than for xylazine. As selectivity for alpha-2 receptors increases, the greater specificity results in higher potency, especially at central alpha-2 adrenoceptors. Medetomidine is considered 10 times, 7 times, and 6 times more potent than xylazine, clonidine, and detomidine, respectively.[4] However, other nonadrenergic mechanisms are probably implicated in analgesic actions of alpha-2 agonists because the rank potency order of spinal depressant actions on in vitro preparations is the same as their rank analgesic potencies in vivo: dexmedetomidine (medetomidine) > clonidine > detomidine > xylazine,[5–7] which does not coincide precisely with alpha-2 agonists of intermediate specificity. It has also been suggested that differences between the actions of these ligands are attributable to an action at alpha-1 receptors.[5]