

Ketamine pain mechanism

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Pain is communicated from the brain to other parts of the body by the CNS (Central Nervous System) and nerve endings. (Mayer, Mao, Holt, Price, 7731-7736) The ligand-gated ion channels, also referred to as LGICs, or ionotropic receptors, are a group of intrinsic transmembrane ion channels that are opened in response to binding of a chemical messenger. (Collingridge, Singer, 290-296) (Dickenson, 307-309) (Dickenson, Chapman, Green, 633-638)

The ion channel is regulated by a neurotransmitter ligand that is very selective to one or more ions like potassium, sodium, calcium, and chloride. (Kandel, Schwartz, Jessell, 178-180) Such receptors located at synapses converting the chemical signal to an electric signal in the post-synaptic cell. (Connolly, Wafford, 529-534) The NMDA receptor (N-methyl-D-aspartate) is such an ionotropic receptor for glutamate. (Dingledine, Borges, Bowie, Traynelis, 7-61) (Lodge, Johnson, 81-86) (Meller, 435-436) By X-ray crystallography, the NMDA receptors have an heterodimer subunits, which are involved in the binding of agonists and antagonists like Ketamine. (Hirota, Lambert, 441-444)

This channel complex contributes to excitatory synaptic transmission at sites throughout the brain and the spinal cord, and is modulated by a number of endogenous and exogenous compounds. (Rabben, Skjelbred, Oye, 1060-1066) NMDA receptors play a key role in a wide range of physiologic and pathologic processes. (Hoffman, Coppejans, Vercauteren, Adriemsen, 240-242) (Klepstadt, Maurset, Moberg, Oye, 513-518) (Coderre, Katz, Vaccarino, Melzack, 259-285) Ketamine is primarily a non-competitive antagonist, which opens in response to binding of glutamate. This NMDA receptor mediates the

reduction of pain effects of ketamine at low doses. (Lofwall, Griffiths, Mintzer, 439-449)

Evidence for this is reinforced by the fact that naxolone, an opioid antagonist, does not reverse the analgesia. Studies also seem to indicate that ketamine is 'use dependent' meaning it only initiates its blocking action once a glutamate binds to the NMDA receptor. (Sorensen, Bengtsson, Ahlner, Henriksson, Ekselius et al., 1615-1621) At high level doses, ketamine has also been found to bind to opioid mu receptors and sigma receptors. Thus, loss of consciousness that occurs may be partially due to binding at the opioid mu and sigma receptors. (Lonnqvist, Norton, 617-621)

(Menigaux, Fletcher, Dupont, Guignard, Guirimand, et al. 129-135) (Koppert, Sittl, Scheuber, Alsheimer, Schmelz, 152-159) (Bushell, Endoh, Simen, Ren, Bindokas, 55-64)

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