The role of GABA in the mediation and perception of pain.

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Source

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Abstract

A great deal of effort has been expended in attempting to define the role of GABA in mediating the transmission and perception of pain. Pursuit of this question has been stimulated by the fact that GABAergic neurons are widely distributed throughout the central nervous system, including regions of the spinal cord dorsal horn known to be important for transmitting pain impulses to the brain. In addition, GABA neurons and receptors are found in supraspinal sites known to coordinate the perception and response to painful stimuli and this neurotransmitter system has been shown to regulate control of sensory information processing in the spinal cord. The discovery that GABA receptor agonists display antinociceptive properties in a variety of animal models of pain has provided an impetus for developing such agents for this purpose. It has been shown that GABA receptor agonists, as well as inhibitors of GABA uptake or metabolism, are clinically effective in treating this symptom. However, even with an enhanced understanding of the relationship between GABAergic transmission and pain, it has proven difficult to exploit these findings in designing novel analgesics that can be employed for the routine management of pain. Work in this area has revealed a host of reasons why GABAergic drugs have, to date, been of limited utility in the management of pain. Chief among these are the side effects associated with such agents, in particular sedation. These limitations are likely due to the simultaneous activation of GABA receptors throughout the neuraxis, most of which are not involved in the transmission or perception of pain. This makes it difficult to fully exploit the antinociceptive properties of GABAergic drugs before untoward effects intervene. The discovery of molecularly and pharmacologically distinct GABAA receptors may open the way to developing subtype selective agents that target those receptors most intimately involved in the transmission and perception of pain. The more limited repertoire of GABAB receptor subunits makes it more difficult to develop subtype selective agents for this site. Nonetheless, a GABAB agonist, CGP 35024, has been identified that induces antinociceptive responses at doses well below those that cause sedation (Patel et al., 2001). It has also been reported that, unlike baclofen, tolerance to antinociceptive responses is not observed with CGP 44532, a more potent GABAB receptor agonist (Enna et al., 1998). While the reasons for these differences in responses to members of
the same class remain unknown, these findings suggest it may be possible to design a GABAB agonist with a superior clinical profile than existing agents. Besides the challenges associated with identifying subtype selective GABAA and GABAB receptor agonists, the development of GABA analgesics has been hindered by the fact that the responsiveness of these receptor systems appear to vary with the type and duration of pain being treated and the mode of drug administration. Further studies are necessary to more precisely define the types of pain most amenable to treatment with GABAergic drugs. Inasmuch as the antinociceptive responses to these agents in laboratory animals are mediated, at least in part, through activation or inhibition of other neurotransmitter and neuromodulator systems, it is conceivable that GABA agonists will be most efficacious as analgesics when administered in combination with other agents. The results of anatomical, biochemical, molecular, and pharmacological studies support the notion that generalized activation of GABA receptor systems dampens the response to painful stimuli. The data leave little doubt that, under certain circumstances, stimulation of neuroanatomically discreet GABA receptor sites could be of benefit in the management of pain. Continued research in this area is warranted given the limited choices, and clinical difficulties, associated with conventional analgesics.

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