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A Pharmacological Study of Dynorphin

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ABSTRACT:

There are numerous types of opioid receptors and endogenous opioids present in the brain. There are other types of opioid receptors, including subtypes of I-' and K (ethylketocyc1azocine), as well as I-' (selective for morphine-like ligands), /) (enkephalins), and K (ethylketocyc1azocine). The enkephalins, 3-endorphin and related substances, and the dynorphins are the three main classes of endogenous opioid peptides, with each subclass having its own unique origins and distributions in the brain. One common misconception holds that all of the major ligand classes are equally selective for all of the key receptor types. A strong affinity for the I-' receptor is found in 3-endorphin, while lj receptors are targeted by enkephalins and K receptors by dynorphin. However, it is doubtful that the action of any of these ligands in vivo is restricted to one form of receptor alone, given they all have high affinity for more than one receptor type, and their extensive eNS distribution. This seems to be especially true of the dynorphins, a family of peptides that evolved from the prodynorphin precursor (proenkephalin B). Many members of this endogenous opioid class interact with high affinity with all three of the major opioid receptor types in the brain, unlike the enkephalins and the endorphins. The fact that they are not analgesic in the brain, though they might be in the spinal cord, makes them practically unique among endogenous opioids.

Keywords*:* Receptor Type, Dynorphin, Amino-Acid, Analgesia, Non-Opioid

INTRODUCTION:

Here, we sum up all we know about the dynorphins' physiology, pharmacology, and behaviour. Since the first dynorphins to be identified (1) and now the best characterised are the 17-amino-acid peptide dynorphin A(2-5) and its 13-amino-acid fragment dynorphin A(6), they will receive special attention. This review places more weight on data than analysis due to the sheer volume of research that are relevant to the topic and the limited space available for presentation.

In Vivo Effects of Dynorphin

BRAIN The ability to provide analgesia in mammals is a hallmark of opioid agonists. However, dynorphin's lack of analgesic effect when injected into the mammalian brain stands

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out. This finding has been validated in other research facilities (7). Very high dosages of dynorphin (8) or specific types of tests have been used in the cases where analgesia was noted (9). Since dynorphin can have a number of motor effects in animals (see further down), it is often required to perform a test for analgesia that does not necessitate the animal's movement, such as vocalisation.

Regulation of prodynorphin processing may also be used to activate the modulatory effects of dynorphin. Some studies suggest that prodynorphin, rather than proenkephalin, is a source of the latter opioid in certain regions of the brain. This dynorphin precursor also contains multiple leucine-enkephalin sequences (10, 11). In this way, the processing steps might directly adjust the ratio of enkephalin to dynorphin in a specific brain region.

Modulatory effects of dynorphin could be activated via regulation of prodynorphin processing as well. Some research suggests that prodynorphin, and not proenkephalin, is the source of the latter opioid in specific brain areas. Multiple leucine-enkephalin sequences are present in this dynorphin precursor (12, 13). Thus, the processing steps may directly affect the enkephalin to dynorphin ratio in a targeted brain region.

Dynorphin, like other opioids, has been proven by multiple researchers to reduce both blood pressure and heart rate (46-48). Some of these research involved the intracerebroventricular injection of dynorphin-(1) or dynorphin-(13), respectively. Dynorphin-(), when administered intravenously, has been shown to augment the effect of morphine on these variables, as reported by Kiang & Wei (14).

However, depending on the place of injection, opioid agonists were shown to either boost or decrease these parameters in a research in which they were administered into the ventral lateral medulla (15). Injecting morphiceptin, DADLE, /3-endorphin, or dynorphin into the pressor regions consistently reduced blood pressure and heart rate, whereas injecting into the depressor regions consistently increased these parameters.

Respiratory depression is one of the most well-known and unwelcome consequences of morphine and other opioid agonists. In morphine-naive animals, dynorphin-(I-13) increased the decrease of respiratory function caused by morphine (16), whereas in morphine-tolerant animals, it antagonised the impact of morphine.

Dynorphin levels are also altered by chronic stress. Millan et al (17) reported that chronic pain resulted in increases in dynorphin in anterior pituitary, thalamus, and spinal cord. Faden et al (18, 19) found that immunoreactive dynorphin levels in the spinal cord rose following local injury, with the increases limited to the site of the injury and correlated in magnitude with the severity of the injury. Specificity of the effect was suggested by the lack of changes in enkephalin levels.

IN VITRO EFFECTS OF DYNORPHIN:

Similar to other opioids, dynorphin modulates neuronal activity throughout the central nervous system. The hippocampus is one of the most thoroughly investigated brain regions

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due to the availability of in vitro and in vivo study models. Researchers have shown that dynorphin-(1-17) has excitatory and inhibitory effects on both spontaneous and evoked activity, and these effects have been shown to be reproducible regardless of pretreatment (20, 21).

Naloxone is commonly used to counteract these effects, while other researchers have shown that inhibition is maintained. There is some evidence that jL and 8 receptors are responsible for the excitatory effects, whereas K receptors are responsible for the inhibitory ones (22).

MOLECULAR BASIS OF DYNORPHIN'S ACTION:

The p, B, and K opioid receptors (morphine, eokephalin, and ethylketocyclazocine, respectively) have been identified as separate classes of opiate receptors in the brains of mammals. Dynorphin- (1-17) and -(1-13) serve as K agonists in the ileum and potentially the spinal cord of the guinea pig, as was previously discussed. However, unlike K agonists, their effect in the brain is more nuanced, and they can modulate the analgesia generated by other opioids despite not being analgesic themselves.

Inhibition of adenylate cyclase (23), calcium and potassium ion channels, and polyphosphoinositide (PI) turnover (24) have all been linked to GTP-binding proteins, indicating yet another putative second messenger for opioid action. Effects of dynorphin on calcium levels could indicate activity via the PI system, which is hypothesised to have a role in intracellular calcium mobilisation (25). While some preliminary research is consistent with the idea that opioids affect PI turnover, more definitive data is needed.

SUMMARY AND CONCLUSIONS:

Dynorphins, like other opioids, are involved in a wide range of physiological processes, including the management of pain, the control of movement, the maintenance of blood pressure and heart rate, the maintenance of normal body temperature, the regulation of metabolism, the regulation of feeding behaviour, the maintenance of hormonal balance, and the reaction to shock or stress. While most opioids have their own effects, the dynorphins are remarkable, if not unique, in that they commonly influence the action of other opioids. Therefore, they do not produce analgesia in the brain, but instead inhibit it in unaccustomed animals while enhancing it in tolerant ones. On their own, they do not significantly alter body temperature or breathing, but they do augment the rapid effects of morphine on these processes. They help reduce stroke risk in a way that is similar to opioid antagonists rather than agonists.

The dynorphins bind to all three of the primary opioid receptor types in the brain, J.L, 5, and K, with a slight preference for K sites, which is consistent with their wide range of physiological effects. Although these sites have been labelled "non-opioid" due to their sensitivity to des-Tyr fragments of dynorphin and/or insensitivity to naloxone, they appear to interact with other physiologically important sites. While binding of dynorphin to a second messenger system has not been definitively linked, various possibilities exist.

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