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MINIREVIEW

INTERACTIONS BETWEEN ANALGESICS AND CALCIUM CHANNEL BLOCKERS

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Abstract—1. The findings, derived from different experimental models, examined in this review, provide evidence that the calcium channel blockers and related drugs possess analgesic effects.

2. The antinociceptive action that some analgesic drugs exhibit may be related to calcium channel blockade.

3. Evidence from a variety of biochemical and pharmacological experimental approaches, support the existence of an interelation between the calcium modulators and the opioid drugs.

4. This idea agrees with the novel neuropharmacological hypothesis that a common very high affinity binding site for multiple neurotransmitters could exist, as has been proposed by Pasternak and Wood (1986).

5. This hypothesis could be extended to the neuromodulators or other neuromediators.

Calcium antagonists are of wide therapeutic use in cardiovascular, pulmonary, neurological and urogenital diseases (Krebs, 1984; Barnes, 1985). A major question is whether or not their effects are due to the same mode of action. In this review, the term calcium antagonists, calcium channel blockers, calcium modulators and calcium entry blockers are used interchangeably.

Recently, the analgesic effect of a calcium modulator nifedepine has been reported by Bustamante *et al.* (1989). In experiments recently performed in this laboratory the analgesic effect of diltiazem, verapamil, nimodipine and Bay K 8644 has been demonstrated (manuscript, in preparation). The same group, using clonixin, a non-steroidal analgesic, reported that this effect of clonixin is not mediated by activation of μ_1, δ- or κ-receptors and they suggest that the antinociceptive effects of clonixin and nifedipine may be associated with the blockade of the transmembrane inward movements of calcium.

Many drugs have been demonstrated to exhibit calcium entry blocking-like activity, v.g. reserpine, has an IC_{50} of about 1 μM, in agreement with Casteels and Longin (1983). Some benzodiazepine derivatives (diazepam and flurazepam) have also been shown to exhibit calcium entry blocking activity (Ishii *et al.*, 1982).

The relationship between calcium modulators and analgesics can be substantiated by several lines of evidence available from the opioid studies. It has been suggested that morphine may enhance the accumulation of free intracellular calcium, thereby increasing potassium conductance. Thus, it is possible that one primary action of opioids may be to increase the intracellular concentration of calcium, as suggested by Duggan and North (1983). Other observations suggest that κ agonists may produce opiate receptor mediated hypothermia through changes in intracellular Ca^{2+} in the hypothalamus (Pillai and Ross, 1986). Also the existence of a mechanism by which dynorphin A inhibits calcium influx and neurotransmitter release has been postulated by Gross and Macdonald (1987).

In a similar way, there are many publications that can be cited to establish a definite relation between calcium modulators and analgesics. Thus, the opioids may be acting at presynaptic or postsynaptic levels in Ca^{2+} entry. The site of action could be deduced from the fact that it has been demonstrated that nifedipine had no effects on presynaptic Ca^{2+} entry, while reducing postsynaptic calcium conductance in nervous tissue (Louvel *et al.* 1986). However, Bay K 8644, a known Ca^{2+} agonist, induces an activated state of the presynaptic calcium channel and this particular state is sensitive to calcium entry blockers (Middlemiss, 1985; Middlemiss and Spedding, 1985). Furthermore, several findings suggests that opioid induced presynaptic inhibition may be related to a decrease in neurotransmitter release coupled to Ca^{2+} fluxes, in agreement with Mudge *et al.* (1979), Furness *et al.* (1980), Tokimara *et al.* (1981) and Katayama and Nishi (1981).

It has been reported that Ca ions antagonize the analgesic effect of morphine. Also the analgesic ED_{50} of morphine was increased when the Ca^{2+} levels were lowered using EGTA, a calcium chelator (Harris *et al.*, 1975). Furthermore, when EGTA was injected intraventricularly, antinociceptive properties were obtained, according to the findings of Schmidt and Way (1980). In addition, administration of calcium or calcium channel antagonists can regulate the analgesic effects of morphine, β-endorphin, fentanyl and other more specific μ and δ opioid agonists, according to the findings of Kakunaga *et al.* (1966), Chapman

and Way (1982), Harris *et al.* (1975), Belger *et al.* (1985), Hoffmeister and Tettenborn (1986), Kavaliers and Ossenkopp (1986, 1987) and Kavaliers (1987). The analgesic effects of morphine, β-endorphin or enkephalines were greatly reduced after injection of Ca^{2+} in the periaqueductal grey region, Guerrero-Muñoz *et al.* (1981). Besides, after acute administration of morphine, a decrease in Ca^{2+} content in the synaptosomes of the brain was obtained, according to Yamamoto *et al.* (1978). Moreover, the synaptosomal Ca^{2+} uptake was decreased after morphine treatment (Guerrero-Muñoz *et al.*, 1979a), consequently, β-endorphin reduced synaptosomal $^{45}Ca^{2+}$ uptake, both *in vivo* and *in vitro*. The responses to morphine and to β-endorphin were completely reversed by naloxone (Guerrero-Muñoz *et al.*, 1979b).

It is worth noting that the effect evoked by the acute administration of opioids, are opposite to those obtained with chronic administration of the same drugs, in accordance to the findings of Harris *et al.* (1976).

The calcium modulators seem to regulate nociception since diltiazem, a calcium slow channel blocker, greatly potentiated and prolonged the antinociceptive effect of morphine in rats. This finding seems to agree with the suggestion that opioid effects on analgesia are exerted via modulation of calcium fluxes across neural membrane (Benedek and Szikszay, 1984). In addition, nifedipine potentiated the analgesic effect of prolactin (PRL) and morphine. Calcium chloride administration antagonized both effects. These data suggest that PRL, similar to morphine, may alter calcium movements across the membrane to produce analgesia, in concordance with the findings obtained by Ramaswamy *et al.* (1986). Besides, TMB-8 (8-(*N,N*-diethylamino)octyl-3,4,5-trimethoxybenzoate), which acts as an intracellular calcium antagonist, induced an antinociceptive effect in the mouse tail-flick test and this response was antagonized by naloxone and by calcium ion. Thus, the activity of TMB-8 resembles that of opioids in that they are antagonized by the same substances *in vivo*, according to the report of Welch and Dewey (1986).

Various experimental findings suggest that the antagonistic effects of Phe-Met-Arg-Phe-amide (FMRF-amide) or the endogenous FMRF-amide-like peptides, on both opiate and opioid-mediated analgesia in mice, may involve alterations in the function of calcium channels, according to the reports of Kavaliers (1987).

The results obtained by Bongianni *et al.* (1986) suggest that Ca^{2+} channel blockers suppress the behavioural and neurochemical expressions of morphine abstinence by a mechanism that is different than those of opioids of α_2-adrenoceptor agonists. Moreover, morphine was found to inhibit, in a dose-related fashion, the calcium fluxes in brain slices and synaptosomes (Crowder *et al.*, 1986).

These results demonstrate that important methodological problems have arisen when opioids and/or calcium blockers were tested as analgesics since their responses do not necessarily provide enough information to allow a wide understanding of their comparative effects. Thus the great variability of the IC_{50} values found could be due to several contributing factors: the time of pretreatment with the drug; the concentration range used; the time and equilibrium on the drug in the tissues. A similar variability in the IC_{50} values of calcium entry blockers in other tissues (rabbit and rat aorta), as inhibitors of NE and depolarization by K-induced contractions, has been reported by Godfraind *et al.* (1986). These variations include values from 0.82 nM for nisoldipine to 10.000 nM for verapamil and from 0.03 nM for nisoldipine to 1.200 nM for diltiazem.

In view of the complexity of events underlying analgesia, interpretation of drug actions based on the antinociceptive properties is difficult. Indeed, inhibition of the noxious stimulus may be due to a decrease in some process in which calcium action is involved. It could also be the result of a change in other ionic processes. Moreover, in spite of their action as calcium modulators, opioids may have multiple electrophysiologic effects at different concentrations. The analgesia could probably be explained by the local anesthetic effect that some calcium modulators exhibit by interacting with Na^+ channels (Rodriguez-Pereira and Viana, 1968; Bayer *et al.* 1975; Galper and Catterall, 1979). It is known that neurons possess both sodium and calcium channels and they have been extensively studied by electrophysiological techniques (Hagiwara and Byerly, 1981; Tsien, 1983). Besides, it has been proposed that the modulated receptor hypothesis, that explains the blockade of Na^+ channels by local anesthetic in nerve and skeletal muscle, could be applied to Ca^{2+} channel blockade by calcium antagonists (Sanguinetti and Kass, 1984). This theory proposes that binding of a drug to a site located within the channel is influenced by the state of the channel and that this state is determined by membrane potential (Hille, 1977).

Recently, it has become apparent that there are distinct subtypes of potential-dependent Ca^{2+} channels in neurons, as described by Bossu *et al.* (1985), Carbone and Lux (1984) and Nowycky *et al.* (1985). The diversity of the kinetic characteristic of calcium currents in various neuronal systems results from the coexistence, in variable proportions, of different types of calcium channels. Some neurons have been shown to possess at least two distinct types of calcium conductances (Miller, 1985), others have described three subtypes of neuronal channels; L, T and N (Nowycky *et al.*, 1985). However, neuronal calcium channels are about equally sensitive to diltiazem and to verapamil but are somewhat different in relation to nifedipine, as reported by Akaike *et al.* (1981), Ito (1982), Ito *et al.* (1984), Brown *et al.* (1984) and Boil and Lux (1985).

In conclusion, neuronal calcium conductances appear to be affected by selective calcium entry blockers, either phenylalkylamines (verapamil), benzothiazepines (diltiazem) or dihydropyridines (nifedipine). These findings have been demonstrated almost exclusively in mammalian systems. Moreover, these calcium modulators may affect other ionic conductances at similar concentrations. If the opioid agents could have some properties related to calcium channel blockers, they may be acting by some of the same mechanisms that the calcium modulators do.

The possibility that opioids and calcium channel blockers could be binding to a similar single class of site in certain tissues of the central nervous system,

could be supported by the findings of Godfraind *et al.* (1986), who using binding techniques, in all tissues examined, including human brain and heart, have revealed that a single site binds dihydropyridines (nitrendipine, nimodipine) reversibly and with high affinity. However, in view of the structural differences between the various classes of opioids and calcium entry blockers it might be expected that their specific binding sites could be distinctly recognized. Moreover, the exact significance of the binding sites for calcium channel blockers found in the C.N.S. remains difficult to assess.

Godfraind *et al.* (1986) suggest that the overall number of observations showing a relationship between α-adrenergic and calcium channels is impressive and while the possibility of overlap between the two entities has been raised, it probably indicates that the coupling between these two structures in the membrane is such that a change in conformation of one, affects the other. A similar relationship could arise between analgesic drugs and calcium modulators.

For calcium entry blockers to be considered a single species, three fundamental factors may account for a selective mechanism of action: (a) that the drug can only be effective as inhibitor if the activation of the tissue is dependent to a significant extent on the entry of extracellular calcium; (b) calcium channels probably do not constitute a single homogenous population in different tissues (Nowycky *et al.*, 1985; Nilius *et al.*, 1985; Hurwitz *et al.*, 1980; Hogestatt, 1984 and Bossu *et al.*, 1985), in consequence, the affinity of different calcium channels for different blockers may vary exhibiting regional tissue differences; (c) the conditions under which voltage-dependent calcium channels are activated play a major role in tissue selectivity. Indeed, the duration and/or frequency of stimulation, as well as the resting potential, will markedly influence the potency of some calcium entry blockers. Based on these facts, the possibility that the analgesic activity may be linked to mechanisms activating calcium influx and intracellular calcium release, in a non-identical manner in all situations, allows the possibility to argue that differences in sensitivity of the calcium channel blockers reflect differences in calcium gating mechanisms, if not in the channel themselves.

Differences of intrinsic activity of calcium modulators might therefore account for apparently selective inhibitory effects of nociception of these drugs. This effect would thus be a property of the agonist and of the receptor with which it interacts, rather than a difference in calcium channels.

The involvement of Ca^{2+} in opioid actions is founded on several experimental observations, exemplified by: (i) Ca^{2+} and its inophores antagonize opioids effects; (ii) Ca^{2+} antagonists enhance opioid antinociception and possess antinociceptive properties; (iii) acute administration of opioids decrease synaptosomal Ca^{2+} content, whereas chronic administration increase the content in nerve ending fraction. All these facts can be used to explain, at least partially, the molecular pharmacology of the dependent Ca^{2+} channels with respect to the analgesic action of opioids. It is hypothesized that nociception is related to the Ca^{2+} levels inside the neuron. Apparently, the lowering of the neuronal calcium content induces analgesia, while the increase produces hyperalgesia. Moreover, with the continuous administration of an opioid, a decrease in analgesia is obtained by the development of tolerance and higher doses are needed to produce analgesia. This situation could reflect an up-regulated Ca^{2+}-modulated-opioid receptor state.

The several findings cited in this review raise the possibility that calcium channel blockers and related drugs, have an analgesic-type effect and that some analgesic drugs may be related with calcium channel blockade or modulation. However, it seems that the effect of both types of drugs is not only due to a simple interaction with calcium channels.

In summary, evidence from a large variety of biochemical and pharmacological experimental approaches, support the existence of an interelation between the calcium modulators and the opioid drugs. This idea is concordant with the novel neuropharmacological hypothesis that a common very high affinity binding site for multiple neurotransmitters could exist, as has been proposed by Pasternak and Wood (1986). This hypothesis could be extended to the neuromodulators or others neuromediators.

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