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COMMENTARY

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Nature's first "atypical opioids": Kratom and mitragynines

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Summary

What is known and objective: Advances in pain research have led to an understanding that many pains are driven by more than one underlying (patho)physiologic cause (ie, they are "multimechanistic") and that better pain relief is obtained with fewer adverse effects when an analgesic is correspondingly multimechanistic. At least two of the more-modern analgesics combine opioid and non-opioid mechanisms, and have become known as "atypical opioids." Less well known is that just as Nature evolved opioids, it also evolved atypical opioids, presaging modern drug discovery efforts.

Comment: Traditional (typical) opioids are extracts or analogs of substances derived from the poppy plant. They produce their analgesic and adverse effects primarily through a single, opioid mechanism (albeit with individual differences). Two most recent analgesics were developed to have both an opioid mechanism and, a second, non-opioid mechanism of action (inhibition of monoamine neurotransmitter reuptake). Little known is that Nature had already evolved a plant source of compounds with the same properties.

What is new and conclusion: As debate about the use and abuse potential of kratom swirls, conflicting, often contradicting, opinions are expressed. A review of the basic pharmacology of kratom reveals the explanation for the bifurcation in viewpoints: kratom has both opioid and non-opioid properties. Fascinatingly, just as the poppy plant (*Papaver*) evolved the typical opioids, *Mitragyna* evolved the mitragynines—Nature's "atypical opioids."

KEYWORDS

analgesic, kratom, neurotransmitter, non-opioid, opioid, pharmacognosy

1 | WHAT IS KNOWN AND OBJECTIVE

Technically, "kratom" is one of the common names for an evergreen tree in the coffee family (*Mitragyna speciosa*) that is native to South-East Asia.[1] But, because of the use of its dried leaves or extract(s) for an energy boost or various medicinal purposes,[2] "kratom" has come to indicate the leaves or other parts of the plant, or even to the active ingredients (Figure 1). As the debate about kratom's postulated therapeutic properties and potential for abuse intensifies, even regulatory agencies take what seems like contradictory points of view regarding kratom's effects, and whether or not it should be scheduled as a controlled substance.[3] The confusion is magnified when attempts are made to classify kratom as either an opioid or a non-opioid. A review of kratom's chemistry and basic pharmacology reveals that it is actually both.[4] More importantly, it reveals that Nature evolved a second plant source of opioids and, further, a natural source of "atypical opioids."

FIGURE 1 Leaves from the kratom plant (*Mitragyna speciosa*)

2 | COMMENTARY

Given the importance of the endogenous opioid system (receptors and transmitters) to so many physiological processes, it is perhaps somewhat surprising that there is only one extant natural source of opioids, *Papaver* (an exception is *Commiphora*, the source of myrrh).[5] The alkaloids morphine, codeine, and thebaine are extracts of the poppy plant, and multiple synthetic and semi-synthetic analogs comprise a family of compounds that display similar characteristics (albeit with individual differences in pharmacokinetics or receptor binding). The therapeutic effects, and most common adverse effects, of the opioids are mediated through activation of three types (and subtypes) of seven-transmembrane G protein-coupled "opioid" receptors.[6] Their mechanism of action is therefore mimicry of endogenous opioid ligands. They relieve pain when an opioid-sensitive mechanism is the cause of the pain, but are not effective when some other mechanism underlies the pain.

2.1 | Multimechanistic pain

The stimulus-to-brain "pain-transmitting" pathways have long been known. Injury at the source releases several chemical mediators that activate a variety of sensory neurons.[7] In particular, primary afferent A-δ (fast-conducting myelinated neurons) and C (slow-conducting non-myelinated neurons) transmit the signal to the dorsal horn of the spinal cord. Secondary afferent neurons mostly decussate and send the signal to higher centres within the brain, where subjective perception is added atop the objective sensation of pain. These pathways have collectively become known as the afferent ("ascending") pain-sensation transmitting pathways. According to this model, all pain is "mono-mechanistic"; that is, transmission goes in a single direction and involves a limited set of neurotransmitters.

Experience suggested, and now research has shown, that the incoming pain signal can be modulated (attenuated)—that is, the presumably same tissue injury gives rise to different sensation/perception of pain. This phenomenon has as its basis pathways that descend from the brain to the spinal cord and synapse on afferent neurons of the ascending pathways. These "descending" pain-sensation modulating pathways in the brain and spinal cord,[8] including DNIC (diffuse noxious inhibitory control) modify the amplitude or temporal characteristics of incoming pain signals.[9] In contrast to ascending pathways, the monoamines norepinephrine and serotonin play prominent neurotransmitter roles in the descending pathways, with variable contributions in different types of pain, at different anatomical sites, and at different periods in the progression or time course (chronification) of pain, depending on the receptors (subtypes) they activate.

Critically, experience and research have shown that many pains involve more than one (patho)physiological process.[10,11] For example, they might be a mixture of a nociceptive component (normal pain detection) and a neuropathic component (aberrant processing). Therefore, treatment of such pains with mono-mechanistic analgesics usually yields suboptimal results (either insufficient pain relief or excess adverse effects). In such cases, better separation of therapeutic from adverse effects can be achieved using analgesics with multiple mechanisms of action that match the multiple mechanisms of pain (patho)physiology.[12,13]

2.2 | "Typical opioids"

The opiates morphine, codeine, and thebaine are derived from *Papaver* and, because of difficult/expensive synthesis, are still extracted from this plant source. All of the commonly used opioids, by definition opiate-like substances, produce similar effects by similar mechanism. The predominant mechanism underlying the analgesic effect of these analgesics is agonist action at MOR (mu-opioid receptor),[14] with individual differences in affinity and efficacy at DOR (delta-opioid receptor), and KOR (kappa-opioid receptor). Some recent compounds in development are more selective for one or another type of opioid receptor, or to the coupling of the receptor with the second-messenger transduction by G protein. There are also individual differences in pharmacokinetic properties and receptor binding, but fundamentally, all of the typical opioid analgesics produce their well-known pain relief and adverse effects through a single, opioid, mechanism—if not, they would not be classified as "opioid" (morphine-like).

For a long time, it seemed that Nature had evolved only a single source for opiates (and by extension opioids), *Papaver*. A minor exception is myrrh, which is derived from *Commiphora* trees and displays typical opioid pharmacology (receptor binding and naloxone reversibility).

2.3 | "Atypical opioids"

Drug discovery efforts aimed at finding analgesics with more favourable properties (eg, greater separation of pain relief from the usual opioid adverse effects) led to first serendipitous, then intentional, drugs that have some opioid pharmacology—but also have

an equally important contribution from a non-opioid mechanism of action.

Buprenorphine and tramadol are examples of analgesics that were found to have multiple mechanisms of analgesic action after their synthesis. Buprenorphine has very high affinity for MOR, which is a major mechanism of its analgesic action.[15] It has been shown to have an additional supraspinal naloxone-, PTX (pertussis toxin)-, and NOP (nociception/orphanin FQ peptide)-insensitive, G_z- and Ser-/Thr-sensitive mechanism, and possibly other contributory mechanisms.[16] Tramadol produces its analgesic effect by the combined action of the enantiomers of parent drug and enantiomers of its *O*-desmethyl (M1) metabolite. Tramadol has at least three mechanisms: affinity for MOR, inhibition of neuronal norepinephrine reuptake (NRI), and inhibition of neuronal reuptake of serotonin (SRI). Tapentadol was chemically engineered to possess strong analgesic efficacy by combining specific dual mechanisms of analgesic action ("directed polypharmacology").[17,18] The two mechanisms are activation of MOR and the inhibition of neuronal reuptake of norepinephrine (MOR-NRI).[19-24] This was accomplished by building on the experience with the weaker analgesic tramadol, with the following major changes: minimize SRI activity; have both analgesic mechanisms reside in a single molecule; and eliminate active metabolite(s). The outcome is that tapentadol is more potent in a variety of animal pain models, and in clinical trials has been shown to have comparable efficacy to oxycodone, with more favourable tolerability.[25-31]

Because of the distinction of these drugs, mechanistically and clinically, from the typical opioids (meaning contributory opioid and non-opioid mechanisms), they have become known as "atypical opioids." Interestingly, these compounds originated in drug discovery laboratories. But unbeknownst to the discoverers of these drugs, Nature had already evolved plants that contain natural substance compounds that possess both opioid and non-opioid properties. The plant source is *Mitragyna* (kratom), and the substances are the mitragynines.[4]

2.4 | Kratom and mitragynines

The dual nature of kratom's pharmacology is apparent in the dual nature of its use by populations where the plant is indigenous (eg, Thailand, Myanmar, Malaysia, Borneo, Sumatra, Philippines, and New Guinea). At low doses (eg, chewed leaves), it is used by labourers to reduce fatigue (cocainelike effect), whereas at higher doses, it is used for a variety of medicinal effects, including pain relief, and recreationally for its sedative and mildly intoxicating effects (opioid-like effect).[32] These seemingly contradictory characteristics have now been explained by multimechanistic opioid (agonist action at opioid receptors) and non-opioid (monoamine neurotransmitter) contributions to its mechanism(s) of action and, indeed, we propose that kratom is Nature's source of "atypical opioids."

Elucidation of the mechanism of action of kratom resulted primarily from a pharmacologic *tour-de-force* by a small group of researchers (Hiromitsu Takayama, Kenjiro Matsumoto, and co-workers and colleagues). Out of the more than twenty alkaloids present in kratom, the main active ingredients are the two indole alkaloids mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG) (Figure 2). The details of their pharmacology have been published and are thus only summarized here:[33-37]

2.4.1 | Opioid pharmacology

- MG and 7-OH-MG bind to opioid receptors with nM affinity (MOR > DOR and KOR) and efficacy (agonist action).
- MG and 7-OH-MG produce antinociceptive effect when administered orally, s.c., or directly into brain ventricles.
- The antinociceptive effect is antagonized by naloxone and the more MOR-selective antagonist cyprodime (but less so by the more DOR- and KOR-selective antagonists naltrindole and nor-binaltorphimine respectively).
- Antinociceptive tolerance develops with 7-OH-MG, as does cross-tolerance to morphine.
- Naloxone precipitates withdrawal signs in 7-OH-MG-tolerant animals, but the withdrawal is milder than that from morphine.

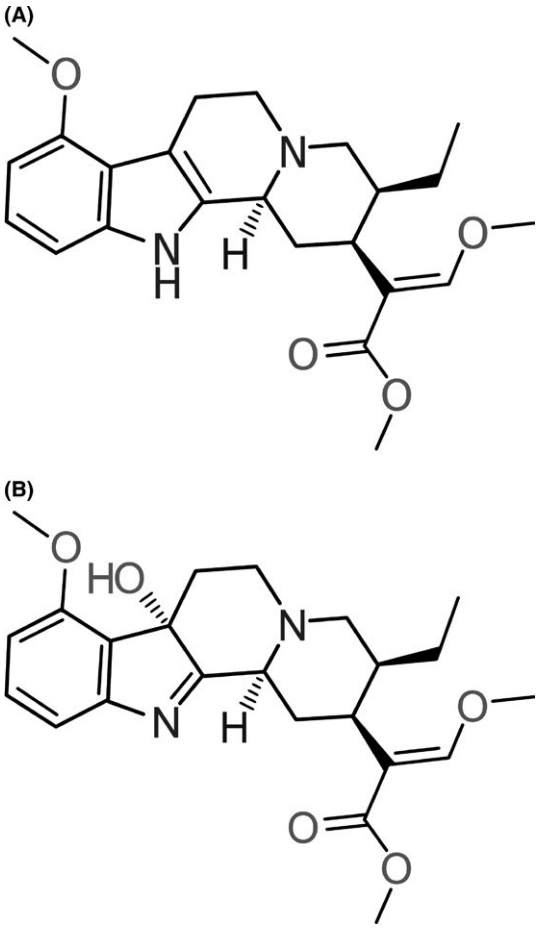

FIGURE 2 Chemical structure of (A) mitragynine and (B) 7-hydroxymitragynine

2.4.2 | Non-opioid pharmacology

- MG interacts indirectly with α_2-adrenoceptors, a known mechanism of analgesic action.
- MG suppresses serotonin-induced head-twitch response in mice, suggestive of a 5-HT_{2A}-related action.
- MG is moderately active in antidepressant tests in mice.
- A role for descending noradrenergic and serotonergic inhibitory systems has been postulated for MG-induced antinociception.

The contribution of the dual components is evident in at least two pharmacologic characteristics:

2.4.3 | Composite pharmacology

- 7-OH-MG is about 5- to 10-fold less constipating than morphine at analgesic doses.
- MG and 7-OH-MG appear to produce less emesis or respiratory depression than does codeine (but further study is needed).

3 | WHAT IS NEW AND CONCLUSION

Extracts of *Mytragyna speciosa* (kratom), particularly of the leaves, have been used for their mildly stimulant, mildly euphoric, and therapeutic effects—including pain relief[32]—for centuries in South-East Asia countries in which the tree is native. With the advent of the Internet, awareness and use of kratom has increased exponentially in other parts of the world, prompting concern by regulatory agencies over issues of product purity control, and potential abuse. The viewpoints about kratom use run the gamut from coffee substitute, aid for withdrawal from opioids, or alternative to opioids for recreational use, to outright ban (as it is in at least six states and some cities in the United States). The US FDA (Food and Drug Administration), DEA (Drug Enforcement Administration), and Congress are trying to reach a consensus on their currently divergent opinions.[3] That there is contrasting viewpoints about the use and potential abuse of kratom is not surprising, since in traditional medicine it has been used for two seemingly disparate purposes: as a mild stimulant to counteract fatigue, and as a mild euphoric.

But it is exactly the apparent dichotomy of kratom's effects and uses that most gives insight into its pharmacology—a clear understanding of which might inform the public and regulatory debate. The major active ingredients of kratom, mitragynine and 7-hydroxymitragynine, have dual mechanisms of action, opioid and non-opioid, producing some opioid-like effects and some non-opioid-like effects.[38] Depending on the dose, its effects can seem more non-opioid-like (low doses), more opioid-like (high doses), or something in-between.

The co-existence of opioid and non-opioid mechanisms of action has recently been recognized as a desirable attribute for an analgesic, increasing the separation between the desired therapeutic and unwanted adverse effects.[39] Current analgesic drugs having such attributes have been termed "atypical opioids." Kratom not only reveals an interesting evolution of another plant source of opioid-like compounds in addition to the opium poppy, but, remarkably, it also shows that Nature was the first source of atypical opioids.

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