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Pain: Identification of novel analgesics from traditional Chinese medicines

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Abstract

The search for analgesics with fewer side effects and less abuse potential has had limited success. A new study from Zhang and colleagues identifies an analgesic alkaloid compound from Corydalis yanhusuo, a traditional Chinese medicinal herb that has a surprising mechanism of action.

Opioids are the gold standard for the treatment of severe acute and chronic pain, but they induce undesirable side effects and drug addiction in many patients. The search for efficacious pain relievers for both acute and chronic pain that do not produce tolerance or dependence has been essentially futile, with few candidates that have been successful in clinical trials. Thus, identification of novel pain therapeutics has been the basis of research and design programs for drug companies for many years. The lack of effective pain relievers has led to a dramatic increase in the use of complementary and alternative medicine [1], and an increase in interest in traditional Chinese medicine (TCM). TCMs, including Chinese herbal medicines, have been used in Asian countries for thousands of years to treat diseases. Recently, an effort to understand the mechanism of TCM treatments has led to the development of the “herbalome”, a database and research library of effective compounds extracted from medicinal plants [2]. New advances in separation techniques are allowing extraction and purification of lipids, carbohydrates and polar compounds that could not be effectively isolated previously [2]. A new study by Zhang and colleagues [3] used a reverse pharmacology approach to screen fractionated samples from 10 TCMs known for their analgesic properties. The samples were tested for their ability to activate the receptor that mediates the analgesic effects of opioids- the mu-opioid receptor. Isolation and purification of an active component identified the alkaloid compound dehydrocorybulbine (DHCB) from *C. yanhusuo*. Surprisingly, DHCB is only marginally effective at opioid receptors, but induces potent, dose-dependent antinociception at non-sedative doses that is insensitive to the opioid antagonist naloxone and thus, is independent of activation of opioid receptors. DHCB analgesia is unaffected by opioid receptor antagonists. DHCB also appears to be an effective analgesic in both inflammatory and neuropathic pain models without inducing tolerance with repeated administration.

The structure of DHCB is similar to another known alkaloid from *C. yanhusuo*, l-tetrahydropalmatine (l-THP), known to bind to dopamine receptors. Zhang and colleagues examined the effects of DHCB and l-THP on dopamine receptor-expressing cells and showed that both compounds were potent antagonists of dopamine receptors. DHCB has high affinity for D2-like receptors compared to D1-like receptors and produces less sedative effects than l-THP at analgesic doses. Similar to l-THP-induced analgesia [4], DHCB analgesia is mediated by D2 receptors. The efficacy of DHCB was tested with multiple pain

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assays including thermal tail-flick and Hargreaves tests, mechanical von Frey test, inflammatory formalin pain test and neuropathic pain in the spinal nerve ligation model. The analgesic effects of DHCB in the tail-flick test were reversed by D2 agonists and abolished in D2-knock-out mice, indicating a role for D2-receptors in modulating thermal pain.

The results are intriguing because they support the idea that dopamine has an important role in pain modulation. There is a long history of studies implicating dopamine in the modulation of pain circuits (reviewed in [5, 6]). Electrical stimulation and lesion of brain areas containing dopamine neurons, such as the substantia nigra and ventral tegmental area, modulate pain. Transgenic mice engineered to be deficient in dopamine have increased sensitivity to pain [7] suggesting that dopamine is important in setting pain thresholds. In humans, D2 receptor binding is associated with pain and pain modulatory capacity [8]. However, a complete understanding of how dopamine modulates pain circuits is not understood as D1 and D2 agonists, as well as D2 antagonists have been demonstrated to be analgesic (reviewed in [5, 6]). The complexity appears to arise from variability in dopamine actions across brain regions, as well as the modality of pain, which can involve different networks [5]. Of particular interest are studies using the atypical antipsychotic amisulpride for effective treatment of burning mouth pain [9] and thermal pain in rodents [10]. Anecdotal clinical evidence suggested for many years that there was a role for atypical antipsychotics in the relief of pain for some patients. A Cochrane review of studies focused on the effectiveness of antipsychotics for pain concluded that antipsychotics produced statistically relevant effects on pain but that many of the studies were small and not well-standardized in pain assessment and documentation [11]. One interesting observation is that low doses of amisulpride are selective antagonists of the D2 autoreceptor [12], the receptor localized presynaptically on dopamine terminals. D2 autoreceptors decrease neurotransmitter release from dopamine terminals. These results suggest that the analgesic action of DHCB may be associated with disinhibition or an increase in dopaminergic and opioid neurotransmission in the midbrain [10].

The possibility that the potent analgesia of DHCB may be a result of selective antagonism of D2 autoreceptors is a provocative interpretation of the data because it implies that selective antagonism of G-protein-coupled receptors (GPCRs) localized to presynaptic domains of neurons may be useful therapeutic targets. In addition, the hypothesis is based on the assumption that ligand-receptor interactions are different and can be exploited for differential activation or inhibition of receptors in these different cellular compartments. Studies have demonstrated that receptor signaling and modulation of opioid [13] and adenosine [14] receptors is different in presynaptic versus postsynaptic areas of neurons. Indeed, it has recently been demonstrated that the efficacy of clozapine, an atypical antipsychotic, is dependent on presynaptic activity of the serotonin system [15]. However, most structure-activity screens are performed in cell lines expressing GPCRs and primarily measure changes in the soma; simulating postsynaptic actions. Thus, it may be that assays of presynaptic GPCR activity are necessary to identify compounds that preferentially target presynaptically localized receptors (Figure 1). Alternatively, the key to effective analgesia may be the combined action on D2 and opioid receptors shown for both DHCB and amisulpride [10]. The idea that drugs can be more efficacious if they have multiple targets or target “network pharmacology” is becoming more mainstream and challenges the traditional drug discovery paradigm of “one gene, one target, one drug” [16]. This may be one reason that TCM has such a long-standing history in the treatment of diseases.

The study by Zhang and colleagues [3] has outlined a strategy for identification and development of pain therapeutics from TCM. Their results support the feasibility of the herbalome project to identify novel pain therapeutics. It is clear that there are many areas of the strategy that can be further optimized. First, there is a need to further develop extraction

techniques and purification techniques. Recent advances have allowed the extraction and fractionation of lipid-like molecules that were typically discarded [17]. These technical advances have inspired the “herbalome project” to intensely focus on developing new extraction and purification techniques [2]. Second, the strategy used in the current study was to screen fractions on mu-opioid receptor-expressing cell lines and it was only fortuitous that DHCB had weak actions at the mu-opioid receptor. Other equally efficacious compounds may have been missed by the selective nature of the screen. Additional high-throughput strategies need to be developed that also screen compounds for their activity at presynaptic receptors and potentially their ability to induce antinociception.

A remaining question is whether target-based strategies are useful for development of new therapeutics. This strategy has been the predominant strategy over the past 20 years and has failed to develop sufficient new therapeutics [18]. Reverse pharmacology is dependent on screening known receptor structures, even though some of the receptors are orphan receptors with no known endogenous ligand.

The pain community has at least expanded their target-based approach to include therapeutic development of ligands that target other proteins including ion channels, such as TRPV1 [19] and transporters, such as the potassium-chloride cotransporter (KCC2) [20] for analgesia. This field is currently exploding and it is likely that natural compounds from TCMs will be isolated that selectively modulate these targets as well.

References

1. Nahin, RL.; Barnes, PM.; Stussman, BJ.; Bloom, B. National health statistics reports. Vol. 18. Hyattsville, MD: National Center for Health Statistics; 2009. Costs of Complementary and Alternative Medicine (CAM) and Frequency of Visits to CAM Practitioners: United States, 2007.
2. Zhang X, Liu Y, Guo Z, Feng J, Dong J, Fu Q, Wang C, Xue X, Xiao Y, Liang X. The herbalome--an attempt to globalize Chinese herbal medicine. Analytical and bioanalytical chemistry. 2012; 402:573–581. [PubMed: 22089819]
3. Zhang Y, Wang C, Wang L, Parks GS, Zhang X, Guo Z, Ke Y, Li K-W, Kim MK, Vo B, et al. Reverse pharmacology on traditional Chinese medicine: Discovery of the analgesic properties of dehydrocorybulbine. Curr Biol. 2013
4. Chu H, Jin G, Friedman E, Zhen X. Recent development in studies of tetrahydroprotoberberines: mechanism in antinociception and drug addiction. Cell Mol Neurobiol. 2008; 28:491–499. [PubMed: 17710533]
5. Wood PB. Role of central dopamine in pain and analgesia. Expert review of neurotherapeutics. 2008; 8:781–797. [PubMed: 18457535]
6. Altier N, Stewart J. The role of dopamine in the nucleus accumbens in analgesia. Life Sci. 1999; 65:2269–2287. [PubMed: 10597883]
7. Hnasko TS, Sotak BN, Palmiter RD. Morphine reward in dopamine-deficient mice. Nature. 2005; 438:854–857. [PubMed: 16341013]
8. Hagelberg N, Martikainen IK, Mansikka H, Hinkka S, Nagren K, Hietala J, Scheinin H, Pertovaara A. Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. Pain. 2002; 99:273–279. [PubMed: 12237205]
9. Maina G, Vitalucci A, Gandolfo S, Bogetto F. Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome: a single-blind study. J Clin Psychiatry. 2002; 63:38–43. [PubMed: 11838624]
10. Weizman T, Pick CG, Backer MM, Rigai T, Bloch M, Schreiber S. The antinociceptive effect of amisulpride in mice is mediated through opioid mechanisms. Eur J Pharmacol. 2003; 478:155–159. [PubMed: 14575800]
11. Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. The Cochrane database of systematic reviews. 2013; 8:CD004844. [PubMed: 23990266]

12. Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, Curet O, Oblin A, Gonon F, Carter C, Benavides J, et al. Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. J Pharmacol Exp Ther. 1997; 280:83–97. [PubMed: 8996185]

13. Fyfe LW, Cleary DR, Macey TA, Morgan MM, Ingram SL. Tolerance to the antinociceptive effect of morphine in the absence of short-term presynaptic desensitization in rat periaqueductal gray neurons. J Pharmacol Exp Ther. 2010; 335:674–680. [PubMed: 20739455]

14. Wetherington JP, Lambert NA. Differential desensitization of responses mediated by presynaptic and postsynaptic A1 adenosine receptors. J Neurosci. 2002; 22:1248–1255. [PubMed: 11850452]

15. Yadav PN, Abbas AI, Farrell MS, Setola V, Sciaky N, Huang XP, Kroeze WK, Crawford LK, Piel DA, Keiser MJ, et al. The presynaptic component of the serotonergic system is required for clozapine's efficacy. Neuropsychopharmacology. 2011; 36:638–651. [PubMed: 21048700]

16. Zhang GB, Li QY, Chen QL, Su SB. Network pharmacology: a new approach for chinese herbal medicine research. Evidence-based complementary and alternative medicine: eCAM. 2013; 2013:621423. [PubMed: 23762149]

17. McCurdy CR, Scully SS. Analgesic substances derived from natural products (natureceuticals). Life Sci. 2005; 78:476–484. [PubMed: 16216276]

18. Sams-Dodd F. Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift. Drug discovery today. 2013; 18:211–217. [PubMed: 23131208]

19. Haanpaa M, Treede RD. Capsaicin for neuropathic pain: linking traditional medicine and molecular biology. Eur Neurol. 2012; 68:264–275. [PubMed: 23037991]

20. Gagnon M, Bergeron MJ, Lavertu G, Castonguay A, Tripathy S, Bonin RP, Perez-Sanchez J, Boudreau D, Wang B, Dumas L, et al. Chloride extrusion enhancers as novel therapeutics for neurological diseases. Nat Med. 2013; 19:1524–1528. [PubMed: 24097188]