DHE Pharmacology Revisited: Does a Broad Receptor Profile Molecule Treat the Whole Migraine?

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Introduction

The Whole Migraine: Phases of the Migraine Cycle

- Migraine is a complex and multifaceted disorder with 5 distinct phases; therefore, it is important to consider treating the whole migraine (**Figure 1**)[1]

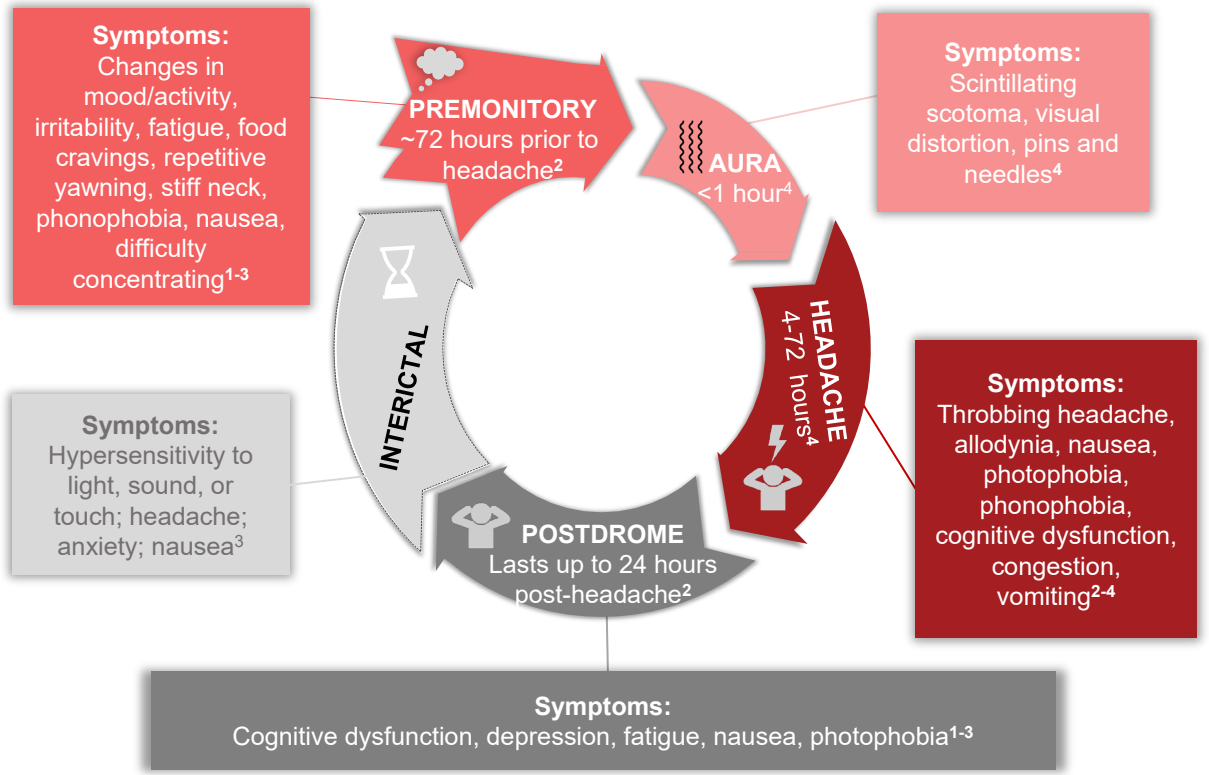
Current Migraine Therapies and Limitations

- One of the primary goals for the treatment of migraine attacks includes the rapid relief of pain and associated symptoms[5]
- Most migraine therapies target a very narrow set of receptors focused mainly on headache pain
  - Triptans are commonly used as acute medications and are 5-hydroxytryptamine (5-HT)$_{1B/1D}$ receptor agonists with some affinity for the 5-HT$_{1F}$ receptor subtype[6]
  - Novel emerging acute and preventive therapies include ditans (5-HT$_{1F}$ receptor agonists), gepants (calcitonin gene-related peptide [CGRP] receptor antagonists), and anti-CGRP monoclonal antibodies[6]
- Because migraine encompasses a spectrum of symptoms, this narrowly targeted receptor profile of most migraine therapies does not allow patients to achieve a holistic relief from migraine, and patients often discontinue treatment due to a lack of efficacy and adverse events[1,7]

Dihydroergotamine (DHE)

- DHE has a long, established history as an effective migraine therapy and is well regarded by physicians because of its[8,9]:
  - Rapid onset[10,11]
  - Efficacy against a full range of acute symptoms of migraine, including pain, photophobia, and phonophobia[12]
  - Efficacy irrespective of the time of treatment[13]
- DHE is effective in patients with difficult-to-treat migraine[9], such as those who have status migrainosus[8], wake up with migraine[14], are triptan resistant[14], have allodynia[12,14], or have severe or prolonged migraine[10,12,14]
- There is minimal risk of medication overuse with DHE[8]
- DHE can slowly dissociate from some target receptor sites, which may explain why DHE has sustained anti-migraine effects, extended duration of benefit, and reduced rates of headache recurrence and medication overuse headaches[8,15]

Figure 1. The Five Phases of the Migraine Cycle Include the Premonitory, Aura, Headache, Postdrome, and Interictal Phases[1-4]



Objective

- To examine comparative receptor pharmacology of various acute therapies for migraine and update the understanding of DHE mesylate pharmacology utilizing an *in vitro* screening approach
- To determine the functional receptor activity of DHE mesylate utilizing an *in vitro* screening methodology

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Methods

- *In vitro* screening for functional receptor activity of DHE mesylate was screened against 168 G protein-coupled receptors using the gpcrMAX Assay Panel, which encompasses 60 distinct receptor families
- A radiolabeled ligand assay was also used to evaluate the binding of DHE mesylate (0-300 nM) to the 5-HT_3 and 5-HT_{4E} receptors
- A literature review of the pharmacology of currently approved acute treatments for migraine was performed

Screening of G Protein-Coupled Receptors (GPCRs)

- Functional receptor activity of DHE mesylate was screened with the gpcrMAX Assay Panel by Eurofins DiscoverX (Fremont, CA), and was run in both agonist and antagonist modes
- Cells expressing various receptors were incubated with 10 µM DHE mesylate for 30-180 minutes, depending on the specific receptor
- Following incubation, agonist and antagonist activity was calculated by measuring chemiluminescence associated with ß-arrestin recruitment
- Known agonists were used as positive controls
- Agonist activity was considered positive if activity was >30% and antagonist activity was considered positive if inhibition was >50%

Results

- Results from the literature review of the pharmacology of acute therapies for migraine and positive hits from the screening gpcrMAX assay of DHE mesylate may be interpreted as shown in **Table 1**
- DHE mesylate exhibited strong agonist activity at the 5-HT_{1A}, α_{2B}, and CXCR7 receptors and strong antagonist activity at the α_{1B}, α_{2A}, α_{2C}, D_3, D_4, and 5-HT_{1F} receptors
- Further work showed DHE mesylate did not bind to the 5-HT_3 receptor, and did so in a limited capacity to the 5-HT_{4E} receptor, at concentrations up to 300 nM
- A model was created to show where in migraine progression DHE may act to address migraine symptoms based on the DHE mesylate screening data (**Figure 2**)

Table 1. Pharmacological Activity of Acute Therapies for Migraine

Receptor	DHE Mesylate	Triptans[16]	Ditans[16]	Gepants[6]
5-HT_{1A}	Agonist	Agonist		
5-HT_{1B}		Agonist		
5-HT_{1D}		Agonist	Agonist	
5-HT_{1E}			Agonist	
5-HT_{1F}	Antagonist	Agonist	Agonist	
5-HT_{2A}	Agonist			
5-HT_{2B}				
5-HT_{2C}	Agonist			
5-HT_3				
5-HT_4				
5-HT_{5A}	Agonist			
5-HT_6				
5-HT_7				
α_{1A}				
α_{1B}	Antagonist			
α_{2A}				
α_{2B}	Agonist			
α_{2C}	Antagonist			
β_1				
β_2				
β_3				
D_1	Antagonist			
D_{2L}	Agonist			
D_{2S}				
D_3	Antagonist			
D_4				
D_5	Agonist			
CGRP[a]	Antagonist			Antagonist
CXCR7	Agonist			

Agonist
Antagonist
Dual Agonist/Antagonist

[a]This represents CALCR-RAMP2 for the DHE mesylate column.

Note: Functional receptor binding data presented in this table is not a direct comparison, but a review of available, published data on functional receptor binding for gepants, ditans, and triptans. DHE mesylate data is based on a functional screening assay against G protein-coupled receptors using 10 µM DHE mesylate and this preliminary screening data are being investigated further at additional concentrations of DHE mesylate.

5-HT = 5-hydroxytryptamine; α = alpha-adrenergic; β = beta-adrenergic; CALCR-RAMP2 = calcitonin receptor-receptor activity modifying protein 2; CGRP = calcitonin gene-related peptide; CXCR7 = C-X-C chemokine receptor type 7; D = dopamine.

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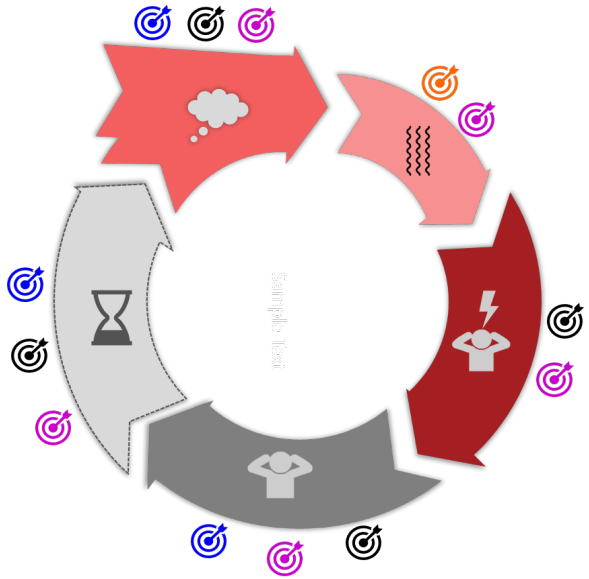
Figure 2. Hypothesis for How DHE May Target the Whole Migraine



KEY

- DHE may alleviate headache pain symptoms via several mechanisms
  - Constrict pain-producing intracranial extracerebral blood vessels via 5-HT_{1B} receptors[17]
  - Alleviates allodynia[12]
  - May lengthen the interictal period and have a beneficial role in migraine prophylaxis due to agonist activity at the 5-HT_{1A} receptor[18]
  - Potentially reverse central sensitization[9]
  - May be involved in repressing CGRP release via activation of α_2-adrenoceptors, which leads to anti-migraine effects[19]
- DHE is effective for acute treatment of migraine with aura[13]
- DHE has 5-HT_{2A} receptor activity, which is involved in mood disorders[20]
- DHE exerts dopamine receptor activity, and a dopamine imbalance during migraine attacks may contribute to pain, discomfort, increased sensory sensitivity, and aversive reactions to environmental stimuli[21,22]

Conclusion

- Unlike other migraine therapeutics, DHE mesylate interacts with several receptor families and subtypes, which include serotonergic, adrenergic, dopaminergic, and CGRP receptor subtypes
- It is suggested that DHE may exert a greater influence than single receptor agonists/antagonists over the pathophysiology of the migraine cycle due to its widespread pharmacological activity
- It is believed that DHE administered at consistent doses and optimal plasma concentrations will not only maximize therapeutic gain, but also improve tolerability and reliability for the patient[8,18,23]
- Advances in non-injected, non-oral delivery systems for DHE hold promise to achieve these goals[8,18,23]

References

1. Charles A. *Headache*. 2013;53:413-419. **2.** Goadsby PJ, et al. *Physiol Rev*. 2017;97:553-622. **3.** Linde M. *Acta Neurol Scand*. 2006;114:71-83. **4.** Headache Classification Committee of the International Headache Society. *Cephalalgia*. 2018;38:1-211. **5.** Lipton RB, et al. *Headache*. 2019;59:1310-1323. **6.** Do TP, et al. *J Headache Pain*. 2019;20:37. **7.** Lipton RB, et al. *Headache*. 2019;59:1762-1772. **8.** Silberstein SD, et al. *Headache*. 2020;60:40-57. **9.** Baron EP, Tepper SJ. *Future Neurol*. 2011;6:327-333. **10.** Saper JR, et al. *Headache*. 2006;46(Suppl 4):S212-220. **11.** Kori SH, et al. *Ann Neurol*. 2010;68(S14).M-41.**12.** Tepper SJ, et al. *Headache*. 2012;52:37-47.**13.** Tepper SJ, et al. *Mayo Clin Proc*. 2011;86:948-955. **14.** Kori SH, et al. *Ann Neurol*. 2010;68(S14).M-48. **15.** Kori S, et al. *J Headache Pain*. 2013;14(Suppl 1):P75. **16.** Rubio-Beltrán E, et al. *Br J Pharmacol*. 2019;176:4681-4695. **17.** Silberstein SD, McCrory DC. *Headache*. 2003;43:144-166. **18.** Cook RO, et al. *Headache*. 2009;49:1423-1434. **19.** Masterson CG, Durham PL. *Headache*. 2010;50:1424-1439. **20.** Marek GJ, et al. *Neuropsychopharmacology*. 2003;28:402-412. **21.** Akerman S, et al. *Cephalalgia*. 2007;27:1308-1314. **22.** Da Silva AF, et al. *Neurology*. 2017;88:1634-1641. **23.** Shrewsbury SB, et al. *Headache*. 2019;59:394-409.

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