Novel receptor activity mapping of methysergide and its metabolite, methylergometrine, provides a mechanistic rationale for both the clinically observed efficacy and risk of fibrosis in patients with migraine

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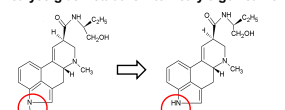
OBJECTIVE

Xoc Pharmaceuticals' objective was to establish, for the first time, a comprehensive and accurate activity profile for the serotonin (5-hydroxytryptamine, or 5-HT) receptor family in terms of activity type, potency, and efficacy for methysergide and its primary metabolite, methylergometrine (also known as methylergonovine) using modern human-cloned receptor assays.

BACKGROUND

The efficacy and safety profile of methysergide in migraine treatment is well described in the literature.[1-21] However, differentiation between the contribution of the drug itself and that of its primary metabolite to the drug's overall effects have never been reported. Xoc developed a detailed receptor activity profile for each compound to enable development of a mechanistic rationale for the efficacy and safety profile of methysergide.

Methysergide Metabolism to Methylergometrine



Methysergide — Methylergometrine

Methysergide is a semi-synthetic ergot alkaloid first developed in the late 1950s. As a specific serotonin receptor antagonist, methysergide was the first and, until the recent introduction of monoclonal antibody calcitonin gene-related peptide (CGRP) inhibitors, the only effective pharmaceutical specifically developed for migraine prevention.[22-26] However, its long-term use diminished chiefly due to risks of retroperitoneal, pleural and cardiac-valve fibrosis.

The original methysergide classification as a "5-HT receptor antagonist" is an oversimplification of the molecule's interaction with the currently known 5-HT receptor families and subtypes and does not provide an adequate basis for understanding the root of the clinical safety observations. Since about 75% of methysergide is metabolized (via the oral route) to methylergometrine, its nitrogen-demethylated derivative, the receptor activity profiles of both the parent and the metabolite must be considered in assessing the clinical impact of the drug's administration.

METHODS

Methysergide and methylergometrine were tested on 13 human recombinant 5-HT G protein coupled receptors found in the central and peripheral nervous systems at EuroscreenFAST laboratory, Belgium. Dose-response curves were generated over the range of 0.01 to 20,000 nM to determine effective concentration (EC_{50}), inhibitory concentration (IC_{50}), and relative agonistic/antagonistic responses.

Serotonin Receptor	Assay	Cell Line	Reference Agonist	Reference Antagonist
5-HT$_{1A}$	GTPγS	CHO-K1	5-carboxamidotriptamine	(S)-WAY 100135
5-HT$_{1B}$	GTPγS	CHO-K1	5-carboxamidotriptamine	Methiothepin
5-HT$_{1D}$	GTPγS	CHO-K1	5-carboxamidotriptamine	Methiothepin
5-HT$_{1E}$	GTPγS	CHO-K1	5-hydroxytriptamine	No reference
5-HT$_{1F}$	GTPγS	CHO-K1	5-hydroxytriptamine	No reference
5-HT$_{2A}$	IPOne	CHO-K1-mt aequorin G$_{\alpha16}$	α-methyl-5-hydroxytriptamine	Ketanserin
5-HT$_{2B}$	IPOne	CHO-K1-mt aequorin G$_{\alpha16}$	α-methyl-5-hydroxytriptamine	Mianserin
5-HT$_{2Cne}$	IPOne	CHO-K1-mt aequorin G$_{\alpha16}$	5-hydroxytriptamine	Methysergide
5-HT$_3$	AEQ	HEK-mt aequorin	5-hydroxytriptamine	MDL72,222
5-HT$_{4E}$	cAMP	CHO-K1	5-hydroxytriptamine	GR113,808
5-HT$_{5A}$	AEQ	CHO-K1-mt aequorin G$_{\alpha16}$	5-carboxamidotriptamine	Methiothepin
5-HT$_6$	cAMP	1321N1	5-hydroxytriptamine	Mianserin
5-HT$_7$	cAMP	CHO-K1	5-carboxamidotriptamine	Risperidone

(S)-WAY 100135 — (S)-N-tert-butyl-3-(4-(2-methoxyphenyl)-piperazine-1-yl)-2-phenylpropanamide
MDL72,222 — Ie,Hi3a,5a-H-tropan-3-yl 3,5-dichlorobenzoate
GR113,808 — (1-(2-(methylsulfonyl-amino)ethyl)-4-piperidinyl)methyl-1-methyl-1H-indole-3-carboxylate

RESULTS

Xoc has generated complete and accurate receptor activity profiles in terms of activity type, potency, and efficacy for methysergide and methylergometrine for the 5-HT receptor families. Xoc has also evaluated receptor activity profiles at the adrenergic and dopaminergic receptors, but neither compound showed significant activity that could contribution to efficacy or side effects.

Serotonin Receptor	Methysergide		Methylergometrine	
	EC_{50}/IC_{50} (nM)	Relative Response	EC_{50}/IC_{50} (nM)	Relative Response
5-HT$_{1A}$	59	Full Agonist	6.1	Full Agonist
5-HT$_{1B}$	33	Full Agonist	2.4	Full Agonist
5-HT$_{1D}$	1.9	Partial Agonist (% Activation = 50%)	0.92	Partial Agonist (% Activation = 70%)
5-HT$_{1E}$	170	Full Agonist	50	Full Agonist
5-HT$_{1F}$	18	Full Agonist	12	Full Agonist
5-HT$_{2A}$	5.1	Full Agonist	0.02	Full Agonist
5-HT$_{2B}$	1.5/1.6	Silent Antagonist (% Activation = 20%)	0.19	Full Agonist
5-HT$_{2Cne}$	1.4	Antagonist	0.89	Full Agonist
5-HT$_3$	None	Inactive	None	Inactive
5-HT$_{4E}$	None	Inactive	None	Inactive
5-HT$_{5A}$	190	Antagonist	6.3	Antagonist
5-HT$_6$	None	Inactive	6.1	Full Agonist
5-HT$_7$	None	Inactive	2.2	Full Agonist

EC_{50} - concentration that induces an activation response halfway between the baseline and maximum after a specified exposure time
IC_{50} - concentration that induces an inhibition response halfway between the baseline and maximum after a specified exposure time
Full Agonist - binds to and activates a receptor with the maximum response that an agonist can elicit at the receptor (% Activation approaches 100%)
Partial Agonist - binds and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist (generally % Activation < 80%)

Methysergide and methylergometrine have similar behavior at all receptors in the 5-HT$_1$ receptor family. Both are partial agonists at the 5-HT$_{1D}$ receptor and full agonists at all of the other 5-HT$_1$ receptors. Methylergometrine is the more potent compound, with significantly lower EC_{50} values, at the 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1E}$ receptors. The compounds show comparable potency at the 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors.

Methysergide and methylergometrine have different behaviors for the 5-HT$_2$ receptor family. Both compounds are full agonists at the 5-HT$_{2A}$ receptor; however, methylergometrine is 250 times more potent than methysergide. While methysergide is a silent antagonist with negligible agonist activity at the 5-HT$_{2B}$ receptor and an antagonist at the 5-HT$_{2C}$ receptor, methylergometrine is the most potent agonist tested by Xoc at both the 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors.

Both compounds are inactive at the 5-HT$_3$ and 5-HT$_{4E}$ receptors and antagonists at the 5-HT$_{5A}$ receptor. While methysergide is inactive at 5-HT$_6$ and 5-HT$_7$ receptors, methylergometrine is a potent full agonist at those receptors.

DISCUSSION

The receptor activity profiles for both the drug methysergide, and its major metabolite, methylergometrine, provide a clear mechanistic rationale consistent with the most significant clinical efficacy and side effect observations associated with methysergide therapy.

Both compounds are agonists at the 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1F}$ receptors, profiles which are reported in the literature to be linked to migraine prevention. In addition, as an antagonist at the 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors, methysergide provides additional mechanistic options that are presented in the literature as being beneficial for migraine prevention.

The receptor profile of methysergide is inconsistent with the mechanistic rationale for causing fibrotic effects and the data suggest that methysergide itself presents a low risk of causing fibrosis. In contrast, methylergometrine, as a highly potent 5-HT$_{2B}$ receptor agonist, has a much higher risk of fibrotic complications. This receptor profile, together with the high rate of methysergide metabolism via the oral route, provides the mechanistic rationale that implicates methylergometrine as the chief risk factor for fibrotic effects associated with this therapy.

Clinical Observation	Physiological Mechanism for Clinical Experience	Methysergide	Methylergometrine
Efficacy (migraine prevention)	5-HT$_{1D}$ receptor agonism	✓	✓
	5-HT$_{1F}$ receptor agonism	✓	✓
	5-HT$_{1B}$ receptor agonism	✓	✓
	5-HT$_{2B}$ receptor antagonism	✓	X
	5-HT$_{2Cne}$ receptor antagonism	✓	X
Fibrotic Side Effects	5-HT$_{2B}$ receptor agonism	X	✓
Psychotic Side Effects	5-HT$_{2A}$ receptor agonism	✓	✓
Vasoconstriction-related Side Effects	5-HT$_{1B}$ receptor agonism	✓	✓

CONCLUSIONS

- The receptor activity profiles for both methysergide and methylergometrine are consistent with their roles as effective migraine prevention agents.
- Methysergide does not have a receptor profile consistent with potential for causing fibrotic effects.
- Methylergometrine, the primary metabolite of methysergide, has a receptor profile consistent with potential for causing fibrotic effects – and is among the most highly potent agents for that activity.

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