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Preclinical Pharmacology of Solriamfetol: Potential Mechanisms for Wake Promotion

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Introduction

- Solriamfetol is a wake-promoting agent (WPA) approved for the treatment of excessive daytime sleepiness associated with narcolepsy (75–150 mg/day) and obstructive sleep apnea (OSA; 37.5–150 mg/day) in the US and EU[1,2]
- The wake-promoting mechanism of solriamfetol may result from dopamine and norepinephrine reuptake inhibition (DNRI)[1,2], but its additional molecular targets are not fully characterized[1,2]
- Preclinical studies in rodents and non-human primates indicate that TAAR1 agonists may have wake promoting properties[6-8]
- Traditional stimulants (e.g. amphetamine) have long been known to activate TAAR1[4,5]

Objective

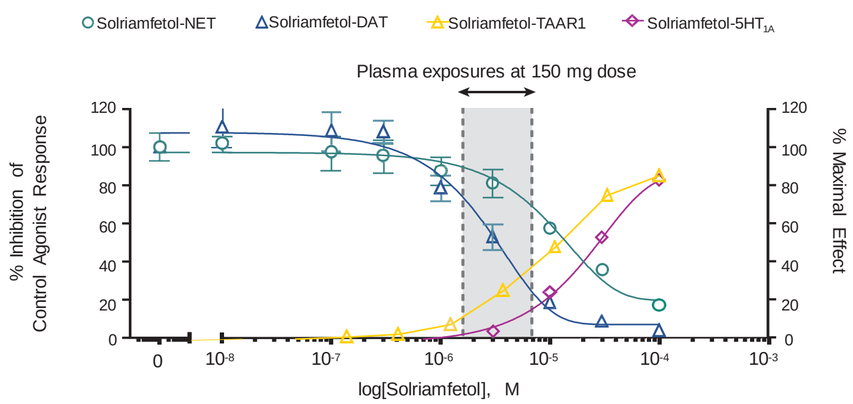
- To understand the molecular targets and effects of solriamfetol *in vitro* and *in vivo* in the context of other WPAs and stimulants

Methods

- *In vitro* binding and functional studies were conducted in a panel of cell lines or membrane preparations expressing transmembrane receptors and monoamine transporters including dopamine and norepinephrine transporters (DAT, NET, respectively), trace amine-associated receptor 1 (TAAR1), and serotonin 1A receptor (5-HT_{1A}) to measure the activity of solriamfetol and comparator WPAs and DNRIs
  - Data for stimulants (eg, amphetamine, methamphetamine) were obtained from published literature
- The firing frequency of ventral tegmental area (VTA) dopaminergic neurons (n=4–8 cells/experiment) in acute slice preparations was recorded using electrophysiology and analyzed
  - Brain slices (250 µm thickness) containing VTA from male C57Bl6/J mice were prepared using standard procedures
  - Slices were perfused with artificial cerebrospinal fluid (aCSF) and spontaneous action potentials were recorded from dopaminergic neurons in current clamp conditions using Axopatch700B and pClamp10 (Axon Instruments)[3]
- Open field locomotor activity was assessed using an automated Omnitech Digiscan (AccuScan Instruments, Columbus, OH)
  - Wild type and $DAT^{-/-}$ mice (n=10/genotype/treatment group) received subcutaneous injections of vehicle or amphetamine (2 mg/kg) followed by solriamfetol (10, 30, or 100 mg/kg); total distance traveled (cm traveled in 90 minutes) was recorded

Results

Figure 1. Solriamfetol is a DNRI that activates TAAR1 and 5-HT_{1A} *in vitro* at clinically relevant plasma concentrations



5-HT_{1A}, serotonin 1A receptor; DNRI, dopamine and norepinephrine reuptake inhibitor; DAT, dopamine transporter; NET, human norepinephrine transporter; hTAAR1, human trace amine-associated receptor 1.

References: 1. Sunosi™ (solriamfetol) tablets Prescribing Information. New York, NY; Axsome Therapeutics, Inc. 2022. **2.** Sunosi™ (solriamfetol) tablets Summary of Product Characteristics. Dublin, Ireland: Jazz Pharmaceuticals Ireland Ltd; 2020. **3.** Revel FG, et al. *Proc Natl Acad Sci U S A.* 2011;108(20):8485-90. **4.** Eshleman AJ, et al. *J Pharmacol Exp Ther.* 1999;289(2):877-85. **5.** Simmler LD, et al. *J Pharmacol Exp Ther.* 2016;357(1):134-44. **6.** Schwartz MD, et al. *Neuropsychopharmacol.* 2017;42:1305-14. **7.** Schwartz MD, et al. Front Pharmacol. 2018 Feb 2;9:35.; 8. Goonawardena AV et al. *Neuropsychopharm* 2019 Jul;44(8):1485-149

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Disclosures: H Gursahani and **W Macfadden** are employees of Jazz Pharmaceuticals. **G Parks** is a former employee of Jazz Pharmaceuticals. **T Jolas, S Cotier, M Martin,** and **S Hughes** have no conflicts to disclose. **G Parks** is a full-time employee of Axsome Therapeutics, Inc. **C Chepke** is a consultant to Axsome Therapeutics, Inc.

Table 1. TAAR1 and 5-HT_{1A} functional activities differentiate solriamfetol from other WPAs

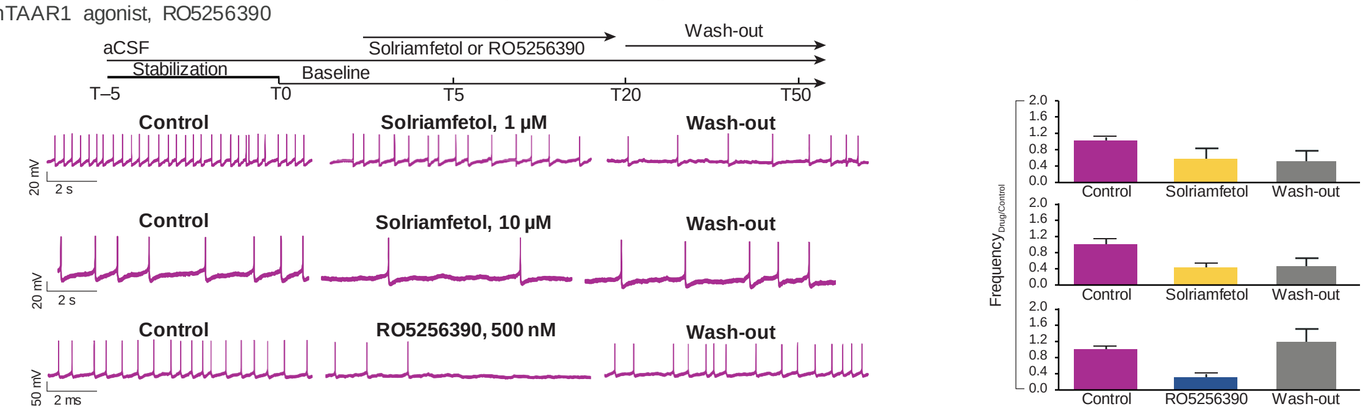
Drug	DAT IC_{50} µM	NET IC_{50} µM	TAAR1 EC_{50} µM (Emax)	$5HT_{1A}$ EC_{50} µM
WPA or hDAT/hNET inhibitor				
Solriamfetol	3.21	14.4	10–16 (100%)	25
Modafinil	2.8	>100	No dose response[a]	Unknown
Bupropion	0.26	2.79	No dose response[a]	No functional activity
Stimulants				
(+) Amphetamine[b]	0.041	0.023	2.8 (91%)	Unknown
(+) Methamphetamine[b]	0.082	0.0013	5.3 (70%)	Unknown

5-HT_{1A}, serotonin 1A receptor; EC_{50}, half maximal effective concentration; Emax, maximal effect; DAT, dopamine transporter; NET, norepinephrine transporter; TAAR1, trace amine-associated receptor 1; IC_{50}, half maximal inhibitory concentration; WPA, wake-promoting agent.
[a]Data based on current studies and confirmed by published literature.[4] [b]Data from published literature.[4,5]

- Solriamfetol and stimulants had TAAR1 activity while modafinil did not
- Solriamfetol had 5-HT_{1A} activity at lower potency
- No additional targets were identified for solriamfetol in a binding assay panel

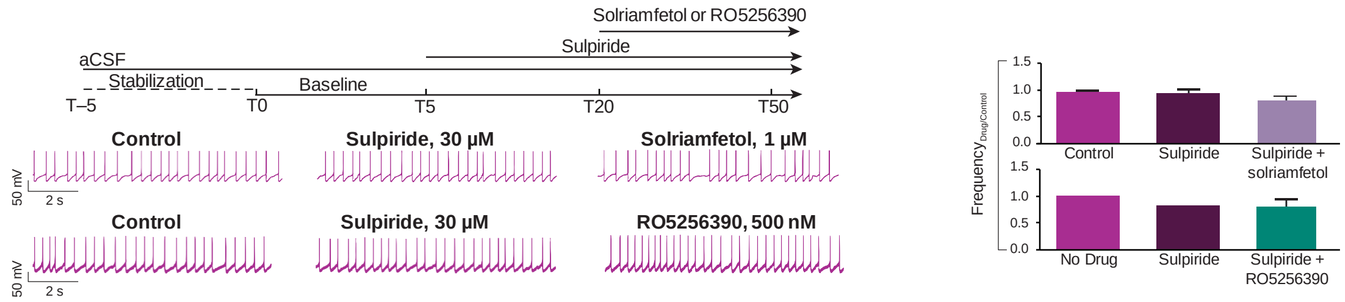
Figure 2. Solriamfetol inhibited firing frequency of VTA neurons in a D2-sensitive manner

- After finding that solriamfetol demonstrated functional activity as a TAAR1 agonist in vitro, it was tested to determine if its activity is consistent with that of a knownTAAR1 agonist, RO5256390



a) Solriamfetol inhibited firing by VTA neurons in a dose-dependent manner, similar to TAAR1 agonist RO5256390

b) Reduction in firing frequency by solriamfetol or TAAR1 agonist RO5256390 was antagonized by pre-treatment with the D2 receptor antagonist sulpiride



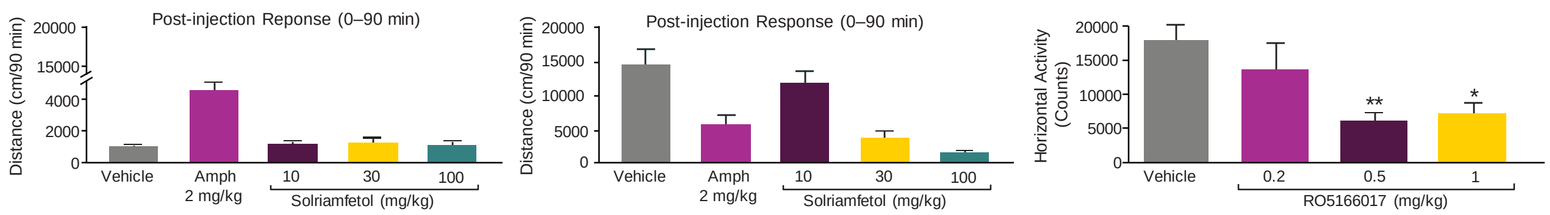
aCSF, artificial cerebrospinal fluid; TAAR1, trace amine-associated receptor 1; VTA, ventral tegmental area.

Figure 3. Solriamfetol inhibited hyperlocomotion in $DAT^{-/-}$ mice

a) Solriamfetol did not increase locomotor activity in wild type mice, unlike a stimulant

b) Solriamfetol reduced hyperlocomotion in $DAT^{-/-}$ mice, similar to a stimulant

c) RO5166017, an established TAAR1 agonist, reduced hyperlocomotion in $DAT^{-/-}$ mice[3]



Amph, amphetamine; DAT, dopamine transporter. *P<0.05 vs vehicle; **P<0.01 vs vehicle.

Conclusions

- Solriamfetol activates TAAR1, a recently recognized component of the endogenous wake-promoting system,[6-7] *in vitro* at potencies that are within the clinically relevant plasma concentration range and overlap with observed DAT/NET inhibitory potencies
  - No TAAR1 activity was observed for the WPA modafinil or the DNRI bupropion
- Solriamfetol shows agonist activity at the TAAR1 receptor and a lower agonist potency at 5-HT_{1A}
  - This activity, in addition to its established activity as a DNRI, may contribute to the wake-promoting effects of solriamfetol[1,2]
- Similar to known TAAR1 agonists, solriamfetol reduced the firing frequency of mouse VTA dopamine neurons in a D2-sensitive manner
- Unlike amphetamine, solriamfetol did not promote hyperlocomotion in naive mice; however, it did dose-dependently inhibit hyperlocomotion in DAT-/- mice, similar to both amphetamine and a known TAAR1 agonist
- Solriamfetol has not been tested in models of schizophrenia or other psychiatric disorders