The Vasopressin $V_{1b}$ Receptor as a Therapeutic Target in Stress-Related Disorders

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Schematic representation of the endocrine, behavioral and autonomic responses to stress mediated by vasopressin (AVP), and the consequences of repeated stress.

The blockade of V₁b receptors in the hypothalamus may prevent the deleterious effects of an hyperactive HPA (stress) axis.
The vasopressin pathways in the brain

- Cortex
- Hippocampus
- Habenula
- Lateral Septum
- Thalamus
- Bed Nucleus of the Stria Terminalis
- Medial Amygdala
- Anterior Hypophysis
- Locus Coeruleus
- Solitary Tract Nucleus

Key:
- PVN: Paraventricular Nucleus of the Hypothalamus
- PHN: Posterior Hypothalamic Nucleus
- SON: Supraoptic Nucleus
- SCN: Suprachiasmatic Nucleus
- Blue: Hypothalamic pathways
- Red: Central Pathways
Immunohistochemical localization of the $V_{1b}$ receptor in the rat brain
Immunohistochemical localization of $V_{1b}$ receptors in brain areas known to modulate anxiety behaviors in rats

- Lateral Septum
- Bed Nucleus of the Stria Terminalis
- Amygdala
- Dendate Gyrus

V1bR

Control
The $V_{1b}$ receptor and stress

Rabadan-Diehl et al., J. Neuroendocrinol. 7: 903-10, 1995

Eight or 14 days immobilization stress or hypertonic saline injection (ip HS) increases $V_{1b}$ receptor mRNA.
SSR149415 : Chemical Structure

Chemical name: (2S, 4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidinecarboxamide, isomer(-)

C$_{30}$ H$_{32}$ Cl N$_3$ O$_8$ S
MW = 630.12
## Selectivity profile of SSR149415 for vasopressin and oxytocin receptors

<table>
<thead>
<tr>
<th>Ki (nM)</th>
<th>V₁b</th>
<th>V₁α</th>
<th>V₂</th>
<th>OT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis</td>
<td>6.0</td>
<td>CHO 1.5 ± 0.8</td>
<td>CHO 91 ± 23</td>
<td>CHO 1412 ± 214</td>
</tr>
<tr>
<td><strong>Rat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis</td>
<td>3.3</td>
<td>CHO 1.3 ± 0.9</td>
<td>Liver 1050 ± 112</td>
<td>Kidney 2897 ± 509</td>
</tr>
</tbody>
</table>

**SSR149415 is selective for the rat and human V₁b receptor**
Efficacy of SSR149415 at the human V$_{1b}$ receptor

Inhibition by SSR149415 of AVP-induced $\text{Ca}^{2+}$ increase in CHO cells transfected with the human V$_{1b}$ receptor.

$\text{IC}_{50} = 3.8 \text{ nM}$

SSR149415 is a competitive antagonist

SSR149415 (M)

Inhibition (% of Control)
Effects of SSR149415 on vasopressin-induced ACTH secretion in conscious rats

SSR149415 decreased in a dose-dependent manner vasopressin-induced secretion of ACTH
Animal models used and psychiatric conditions* modeled to investigate the effects of SSR149415 on emotional processes

- 4-Plate
- Light/dark
- Social Interaction
- Punished Drinking
- Elevated Plus-Maze

- Mouse Defense Test Battery
  - Risk Assessment
  - Flight
  - Defensive Aggression

- Restraint stress-induced ACTH secretion and physiological changes
  - Tail-pinched-induced NE release
    - Social Defeat
    - Conditioned fear
    - Distress vocalizations in rats or guinea pigs

- Forced Swimming
- Chronic Mild Stress
- Chronic social stress

Generalized Anxiety Disorder
Panic Disorder
Acute Stress Disorder
Major Depressive Disorder

*According to the DSM-IV classification (1994)
Second Joint French – Swiss Meeting on Medicinal Chemistry
Beaune, 1-4 July 2003
Effects of SSR149415 in two classical models of anxiety: The elevated plus-maze and Vogel conflict tests in rats

Elevated Plus-maze

Vogel Conflict

SSR149415 produced weak anxiolytic-like activity in the elevated plus-maze and Vogel conflict tests in rats.
Effects of SSR149415 in the elevated plus-maze test in mice following social defeat

SSR149415 antagonized the heightened emotionality in the elevated plus-maze produced by prior (stressful) exposure to an aggressive isolated resident.
The mouse defense test battery

- **FLIGHT**
- **RISK ASSESSMENT**
- **DEFENSIVE AGGRESSION**
Effects of SSR149415 in the mouse defense test battery

SSR149415 reduced defensive aggression, but no other aspects of defensive behaviors
Effects of SSR149415 on offensive aggression in hamsters

SSR149415 reduced both conspecific offensive attack and olfactory investigation in hamsters.
Effects of SSR149415 on maternal separation-induced distress vocalizations in rat or guinea pig pups

**Rat Pups**

SSR149415 produced a dose-dependent decrease in both sonic and ultrasonic distress vocalizations.

**Guinea Pig Pups**

* Fluoxetine

* SSR149415

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Effects of SSR149415 on acute stress-induced ACTH or NE secretion in rats

Restraint Stress-induced increase in plasma ACTH levels

SSR149415 prevented both restraint and tail pinch stress-induced ACTH and NE releases, respectively.

Tail Pinch Stress-induced release in NE in the prefrontal cortex

SSR149415 prevented both restraint and tail pinch stress-induced ACTH and NE releases, respectively.
Effects of SSR149415 in an animal model of depression: The forced-swimming test in rats

SSR149415 produced dose-dependent antidepressant-like activity
The Chronic Mild Stress Procedure in Mice: A model of depression

Chronic sequential application of mild stressors*

Non-stressed mouse

Stressed mouse

Tests

Treatments

1  2  3  4  5  6  7  8  9 weeks

• Restraint
• Water and food deprivation
• Paired housing in damp sawdust
• Light/dark cycle modification
• Forced swimming

*
Effects of repeated treatment (39 days/once a day, ip) of SSR149415 in the chronic mild stress model in mice

Repeated administration of SSR149415 reversed the degradation of the physical state produced by stress.
Effects of 39-day treatment (once a day, ip) of SSR149415 in the chronic mild stress model in mice

Anxiety in the Elevated plus-maze

- NON-STRESSED CONTROLS
- STRESSED CONTROLS

Repeated administration of SSR149415 reversed anxiety produced by stress

Risk Assessment in the Mouse Defense Test Battery

- FLUOXETINE (10 mg/kg)
- SSR149415 (10 mg/kg)
- SSR149415 (30 mg/kg)
Cell proliferation in the hippocampal dentate gyrus of stressed and non-stressed mice

Chronic mild stress decreases the number of BrdU-positive cells

**No stress**

Number of BrdU positive cells per dentate gyrus

- 0
- 1000
- 2000
- 3000
- 4000

**Stress**

24h post BrdU

Chronic mild stress decreases the number of BrdU-positive cells

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Repeated treatment with SSR149415 prevented stress-induced decrease of cell proliferation in the subgranular zone and neurogenesis in the granular cell layer of the dentate gyrus.
Phenotype of BrdU-labeled cells 30 days after the end of stress exposure

The population of surviving BrdU-positive cells essentially mature into neurons.

No difference in phenotypic expression patterns between groups.

Mature neuron: 73%
Glial cells: 9%

![Diagram showing phenotypic expression patterns after no stress, stress, and treatments with SSR149415 and fluoxetine.](image-url)
The Visible Burrow System: A Realistic Model of Depression in Rats
Effects of repeated treatment with SSR149415 on agonistic behavior in socially stressed rats in a visible burrow system

Fighting intensity with the dominant rat

ACTH secretion following restraint stress

Fluoxetine and SSR149415-treated animals showed higher wound counts than did controls rats

SSR149415-treated rats showed much higher plasma ACTH levels relative to vehicle subordinates, suggesting normalization of this HPA axis parameter
Expected clinical spectrum of therapeutic activity of SSR149415 in anxiety/depressive disorders

- Generalized Anxiety Disorder
- Panic Disorder
- Acute Stress Disorder
- Major Depressive Disorder

Benzodiazepines → Tricyclics, SSRIs and mixed 5HT/NARIs → SSR149415
SSR149415 : Safety studies

- Central depressant effects in mice: rotarod, traction test and spontaneous activity
  - No effect up to 100 mg/kg, p.o.

- Sleep pattern in rats: EEG
  - No modification up to 30 mg/kg, p.o.

- Food intake and weight gain: Obese (ob/ob) and Lean female mice, normoglycemic mice and rats
  - No effect up to 30 mg/kg, p.o.
Effects of SSR149415 on spatial memory in mice: The Morris water maze

SSR149415 had no effect on either the acquisition of the test or on recalling the platform position after removal.
Effects of SSR149415 in the forced-swimming test in hypophysectomized rats

SSR149415 is still effective in hypophysectomized rats, indicating that the antidepressant-like effects do not depend on blocking only the hypothalamic V₁b receptors.
Effects of local infusions of SSR149415 in the forced-swimming test in rats

Lateral Septum

Central Amygdala

The antidepressant-like effects of SSR149415 are mediated by the V_{1b} receptors located in the lateral septum and the amygdala.
Conclusion

- The $V_{1b}$ receptor antagonist SSR149415 is able to attenuate some but not all stress-related behaviors in rodents.

- The $V_{1b}$ receptor antagonist showed clear effects only in particularly stressful situations, and in tests sensitive to social or aggression cues.

- SSR149415 is devoid of central depressant effects, even at high doses, and does not affect cognitive processes or food intake, suggesting a large therapeutic window.

- The lateral septum and the central nucleus of the amygdala participate in the antidepressant-like action of SSR149415

- $V_{1b}$ receptor antagonists might be useful as a treatment for major depression and stress disorders that result from traumatic events
Acknowledgments

CHEMISTRY

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ELECTROPHYSIOLOGICAL STUDIES

P. AVENET
M. DECOBERT
D. FRANCON

BEHAVIORAL STUDIES

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