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

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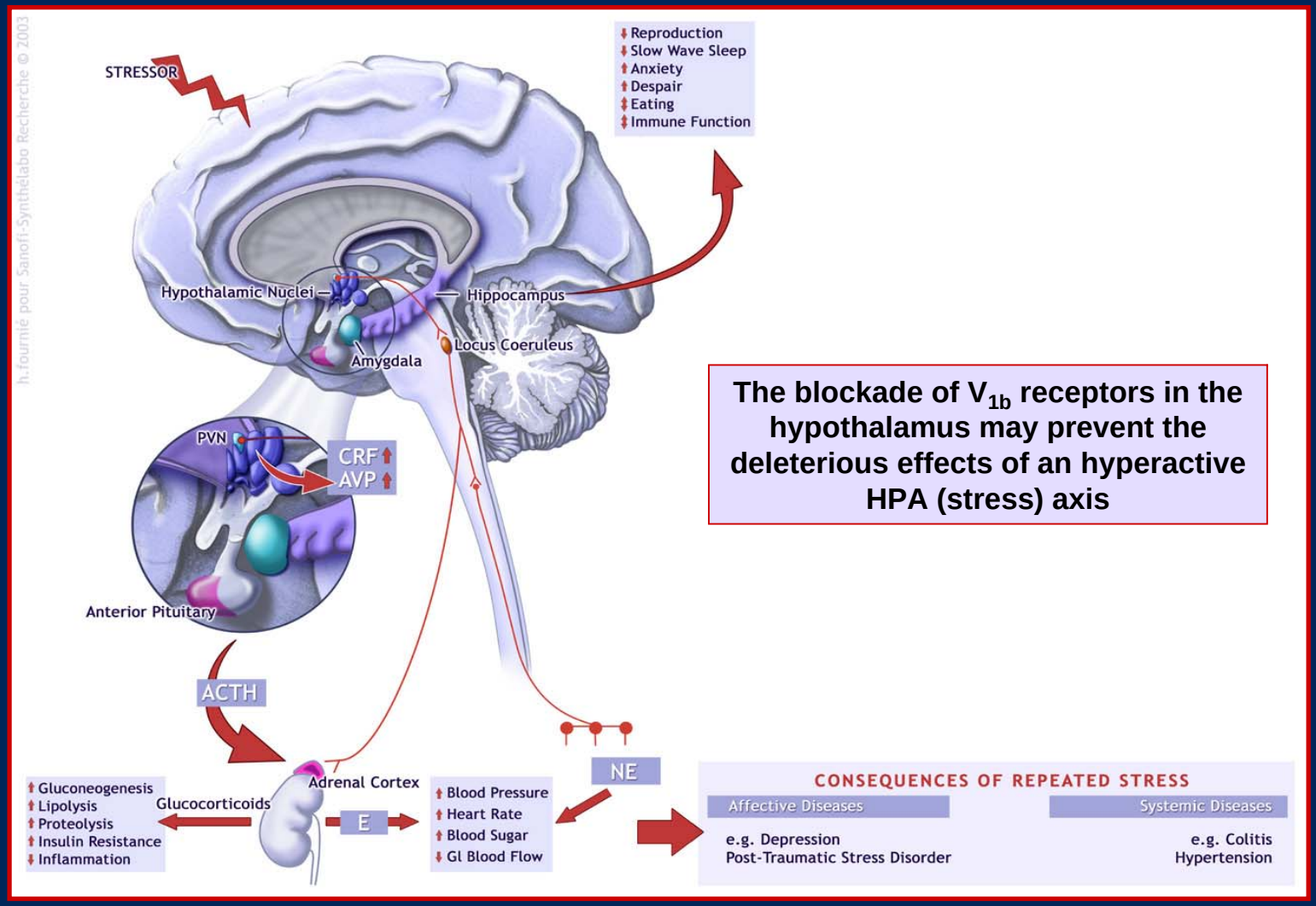
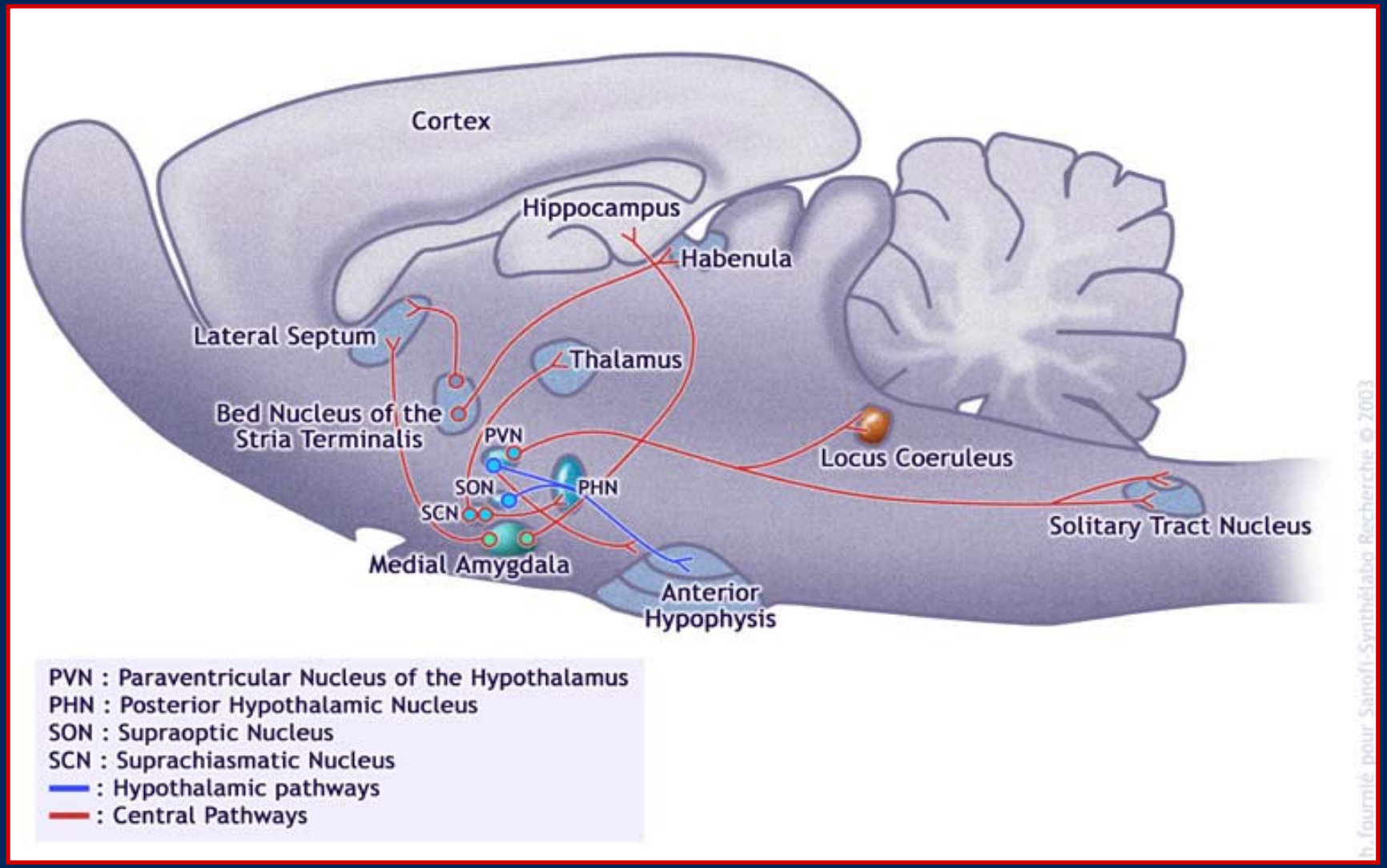
Schematic representation of the endocrine, behavioral and autonomic responses to stress mediated by vasopressin (AVP), and the consequences of repeated stress

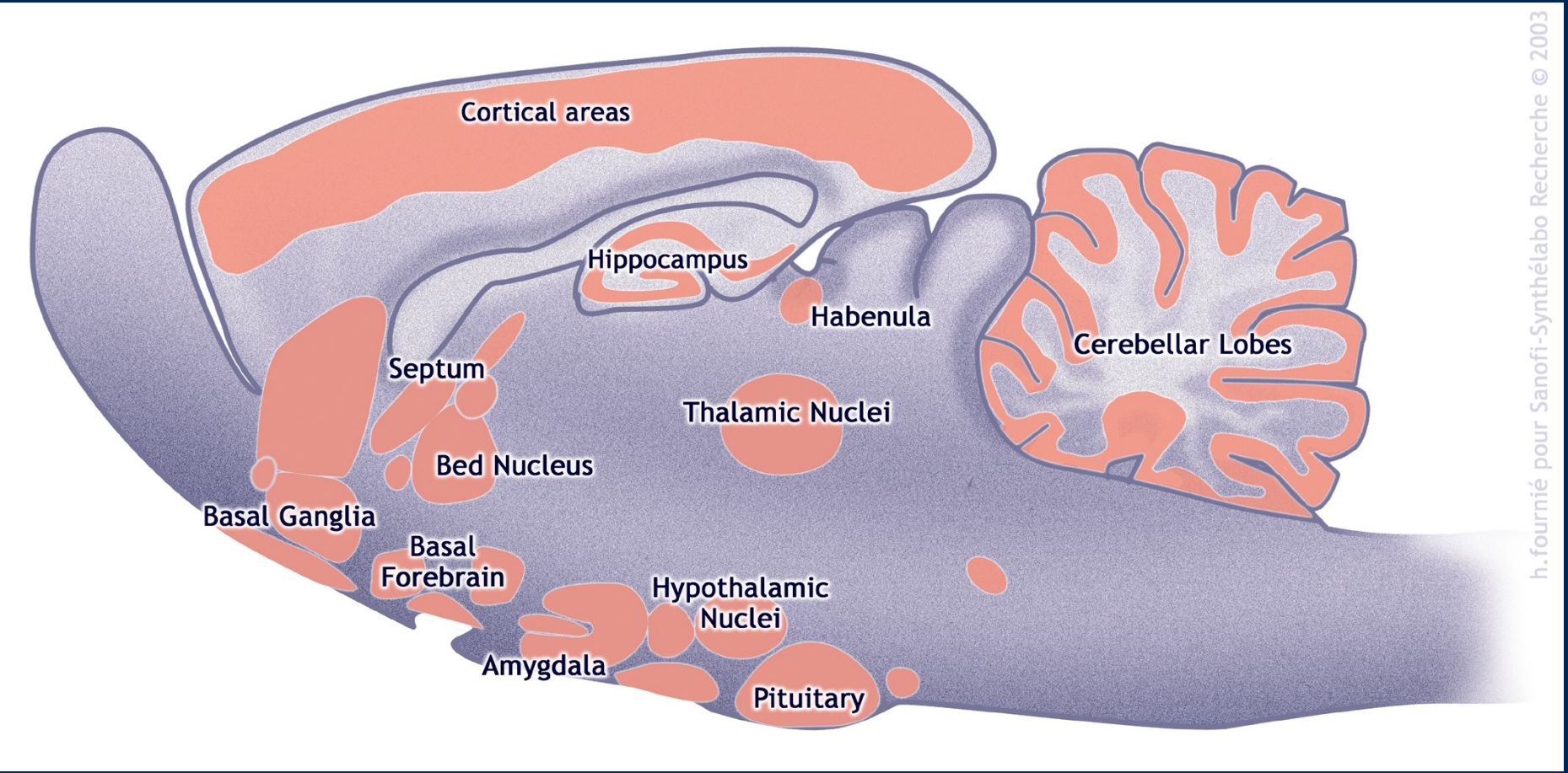


The blockade of V_{1b} receptors in the hypothalamus may prevent the deleterious effects of an hyperactive HPA (stress) axis

The vasopressin pathways in the brain



Immunohistochemical localization of the V_{1b} receptor in the rat brain



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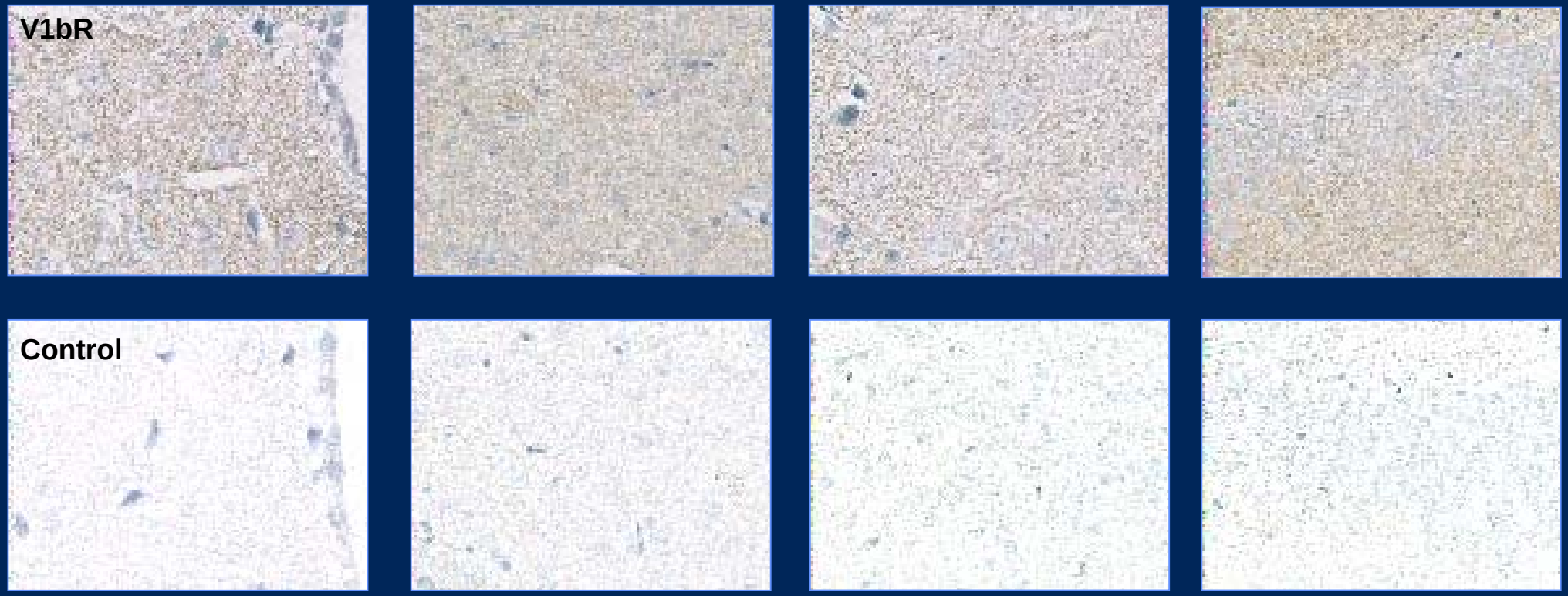
Immunohistochemical localization of V_{1b} receptors in brain areas known to modulate anxiety behaviors in rats

Lateral Septum	Bed Nucleus of the Stria Terminalis	Amygdala	Dendate Gyrus



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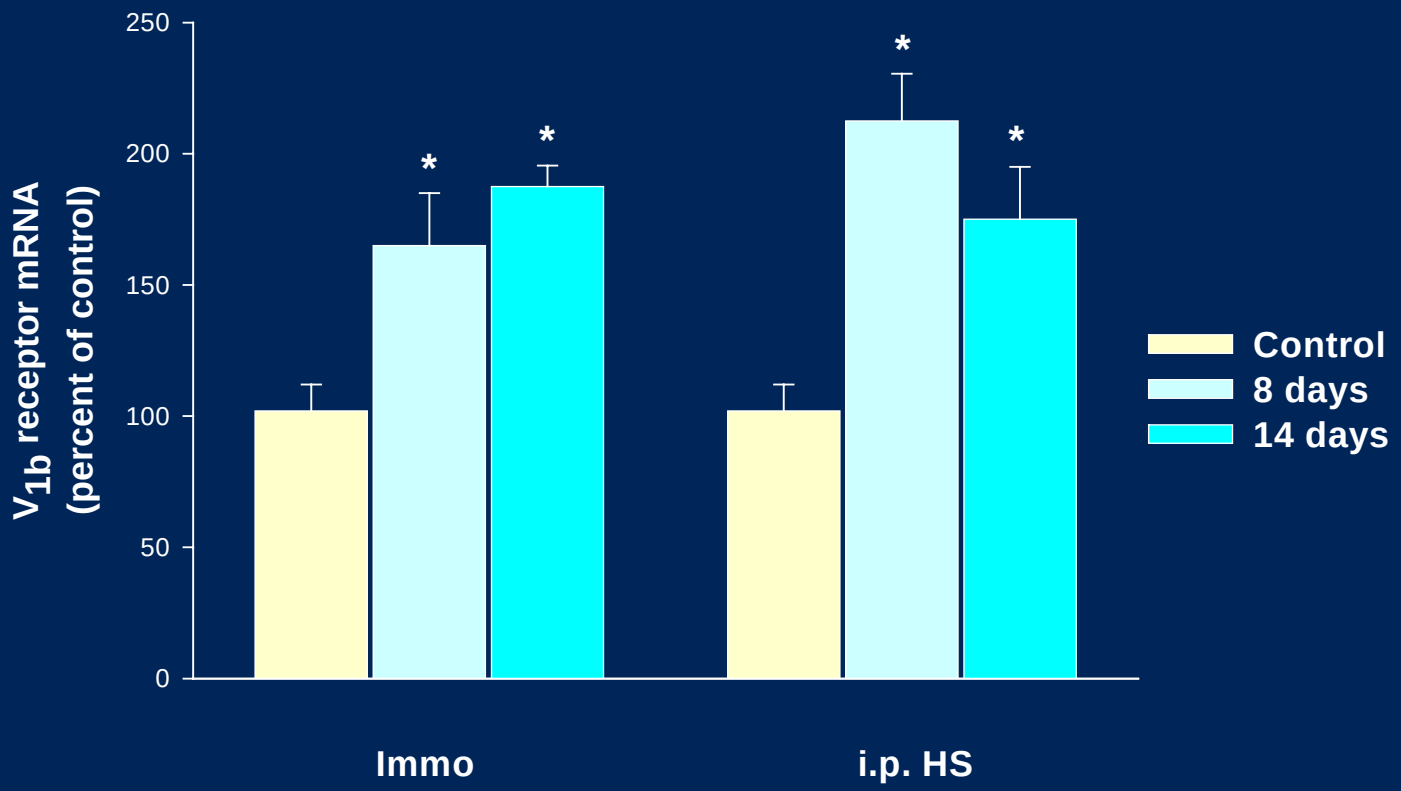
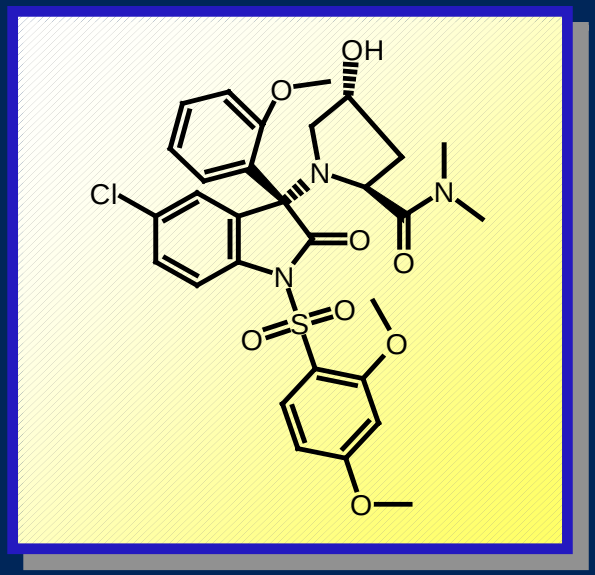
The V_{1b} receptor and stress



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



$C_{30}\ H_{32}\ Cl\ N_3\ O_8\ S$
MW = 630.12

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

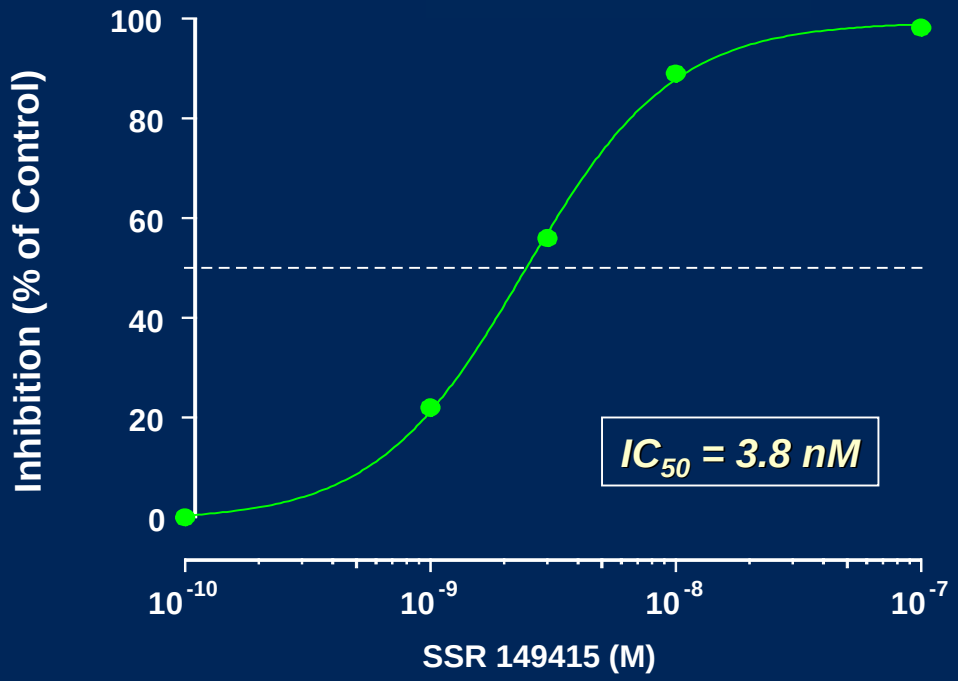
Selectivity profile of SSR149415 for vasopressin and oxytocin receptors

Ki (nM)	V_{1b}		V_{1a}	V_2	OT
Human	Hypophysis 6.0	CHO 1.5 ± 0.8	CHO 91 ± 23	CHO 1412 ± 214	Itk 174 ± 35
Rat	Hypophysis 3.3	CHO 1.3 ± 0.9	Liver 1050 ± 112	Kidney 2897 ± 509	Mammary 270 ± 39

SSR149415 is selective for the rat and human V_{1b} receptor

Efficacy of SSR149415 at the human V_{1b} receptor

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



SSR149415 is a competitive antagonist

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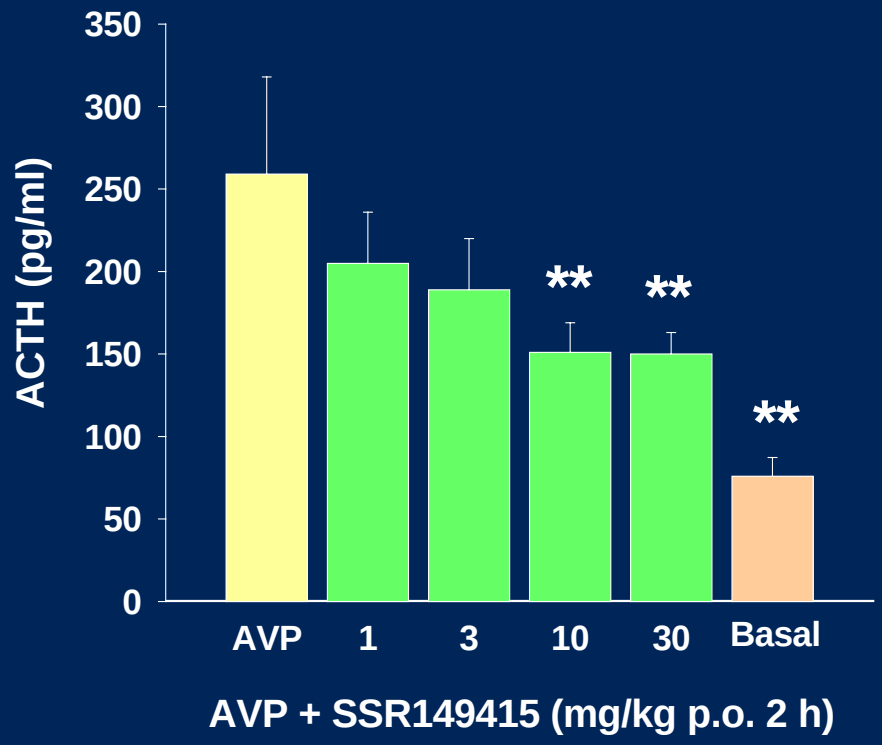
Effects of SSR149415 on vasopressin-induced ACTH secretion in conscious rats



SSR149415 decreased in a dose-dependent manner vasopressin-induced secretion of ACTH

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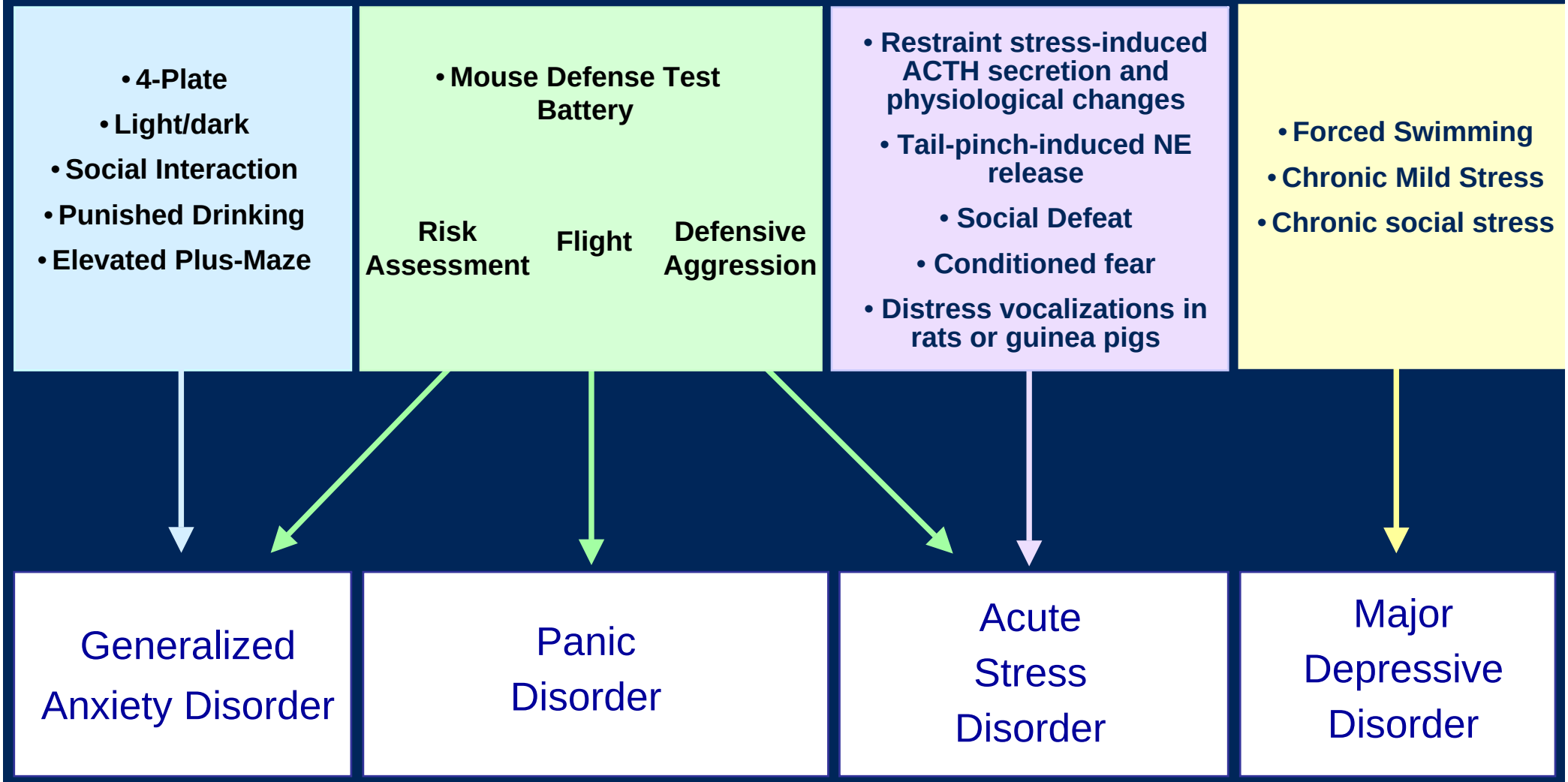
Animal models used and psychiatric conditions* modeled to investigate the effects of SSR149415 on emotional processes



*According to the DSM-IV classification (1994)

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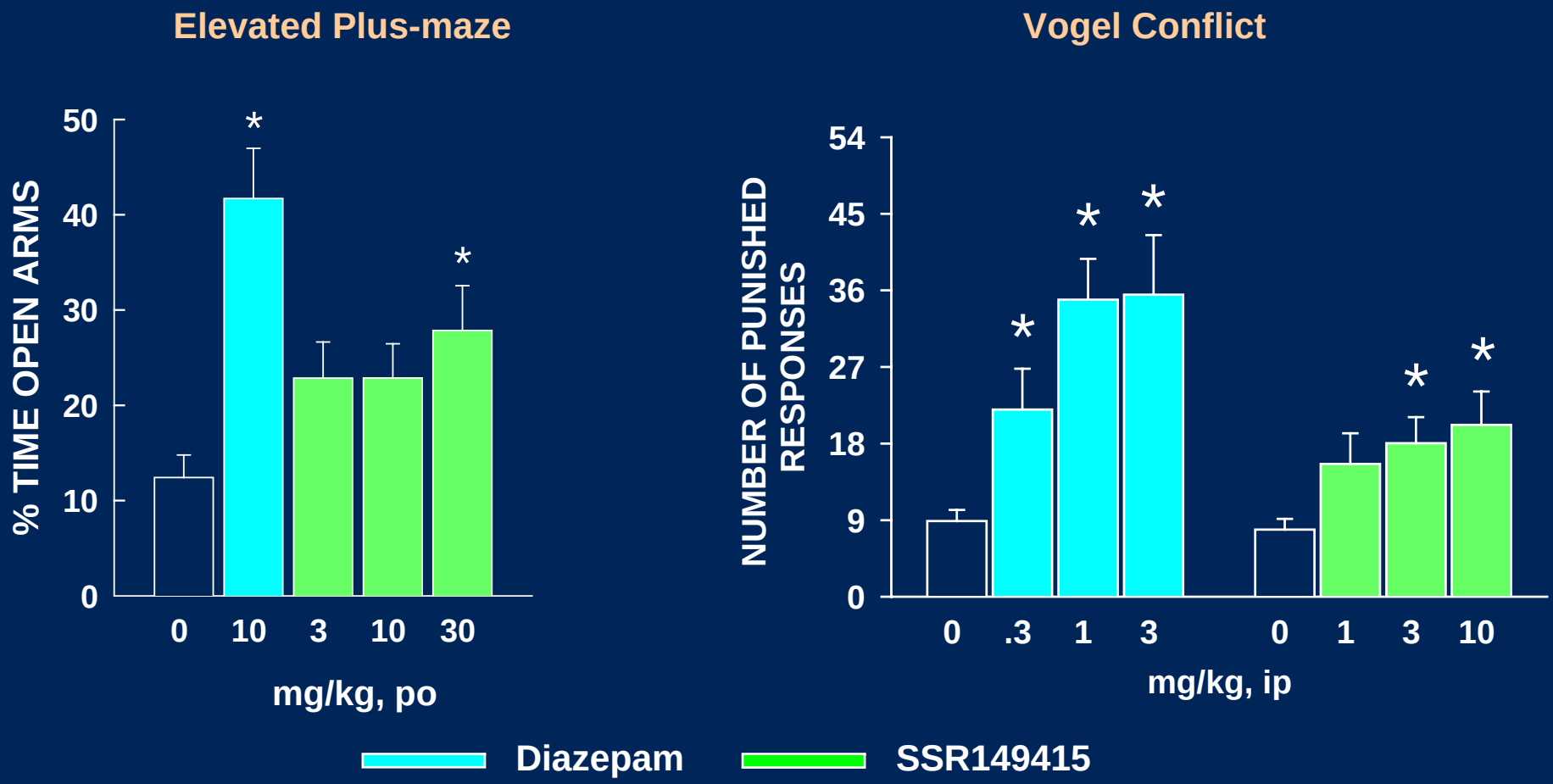
Effects of SSR149415 in two classical models of anxiety: The elevated plus-maze and Vogel conflict tests in rats



SSR149415 produced weak anxiolytic-like activity in the elevated plus-maze and Vogel conflict tests in rats

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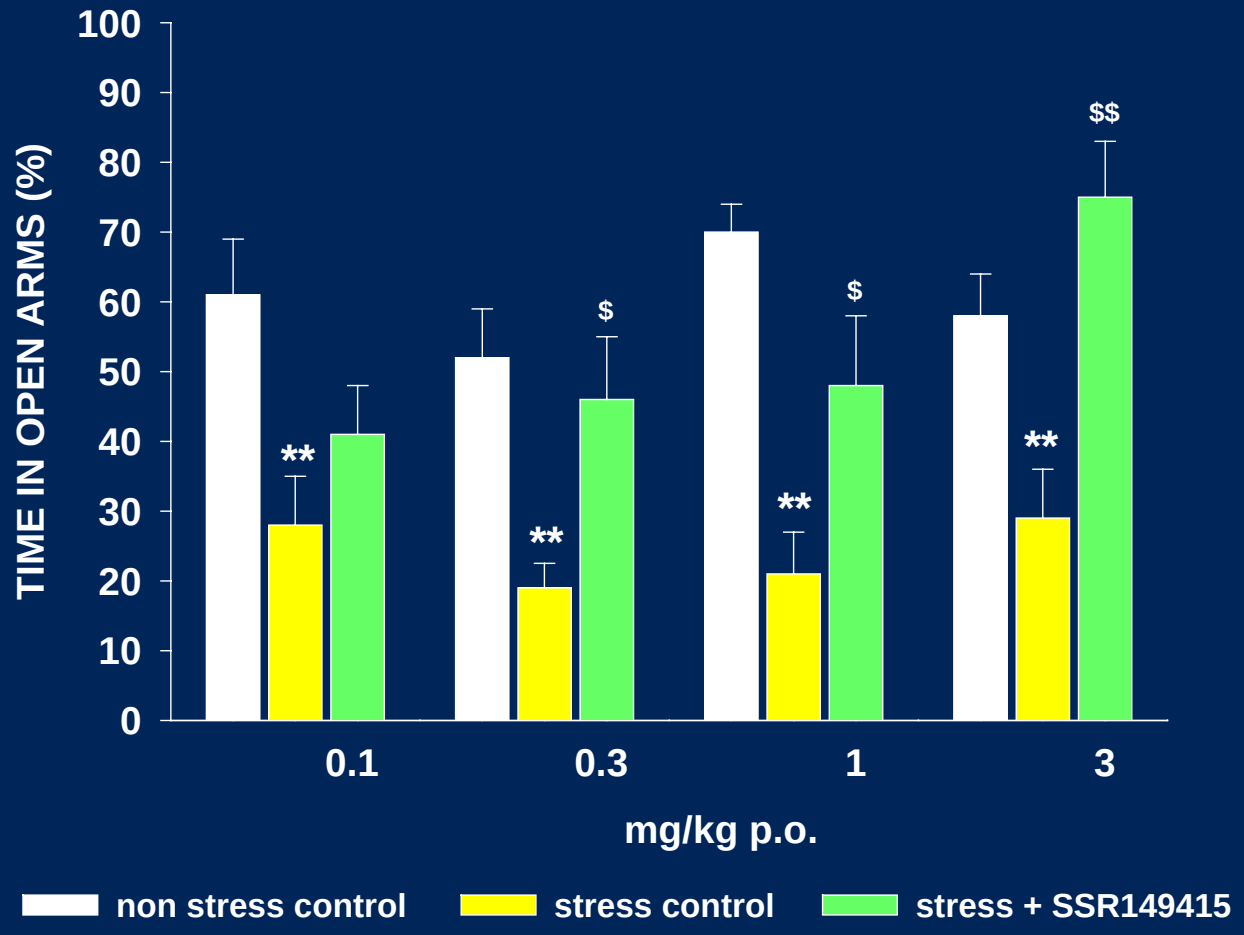
Effects of SSR149415 in the elevated plus-maze test in mice following social defeat



SSR149415 antagonized the heightened emotionality in the elevated plus-maze produced by prior (stressful) exposure to an aggressive isolated resident

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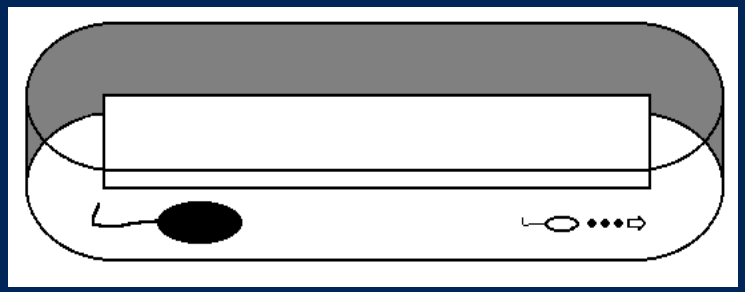
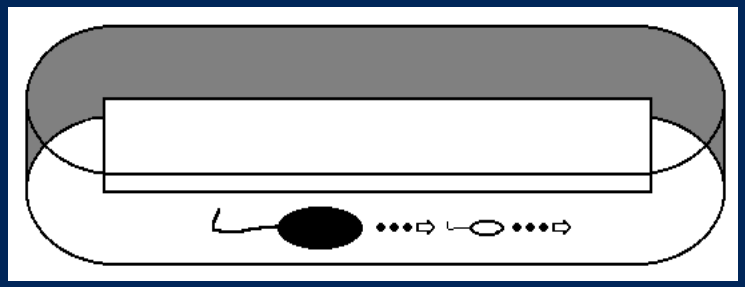
The mouse defense test battery

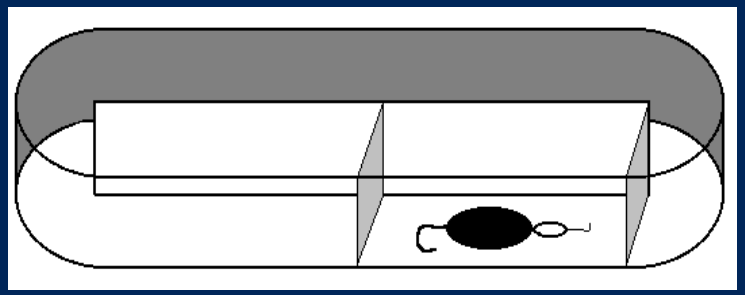
FLIGHT →



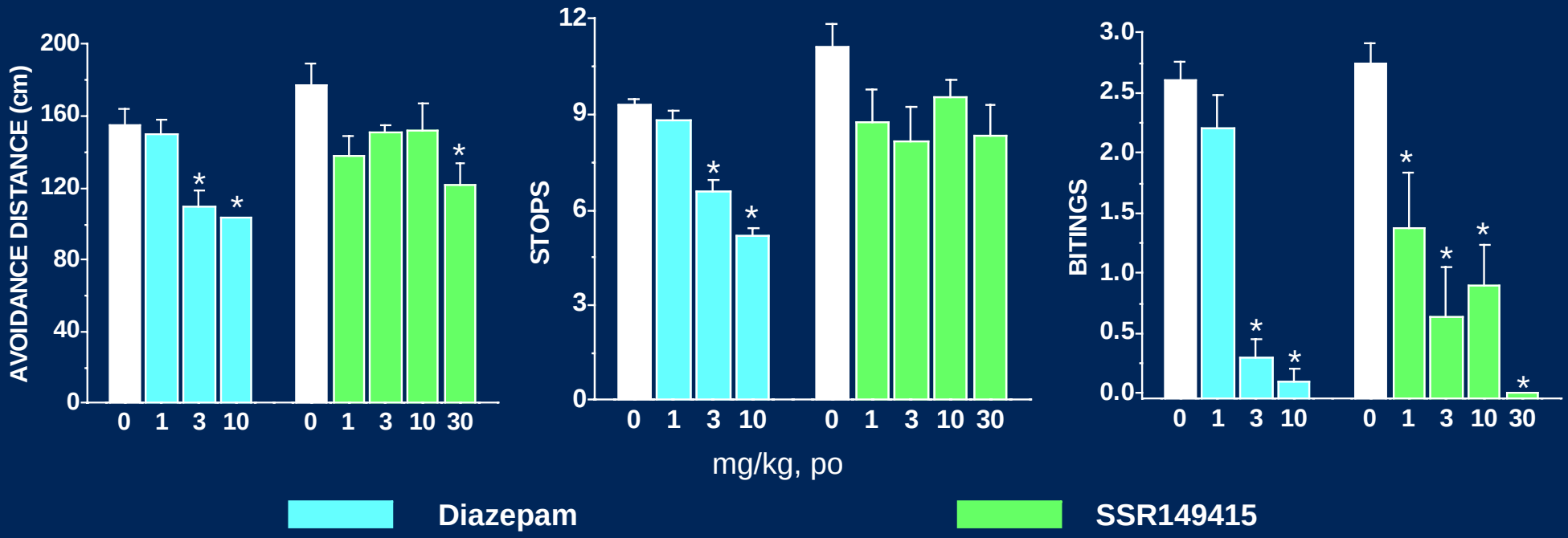
RISK ASSESSMENT →



DEFENSIVE AGGRESSION →



Effects of SSR149415 in the mouse defense test battery



SSR149415 reduced defensive aggression, but no other aspects of defensive behaviors

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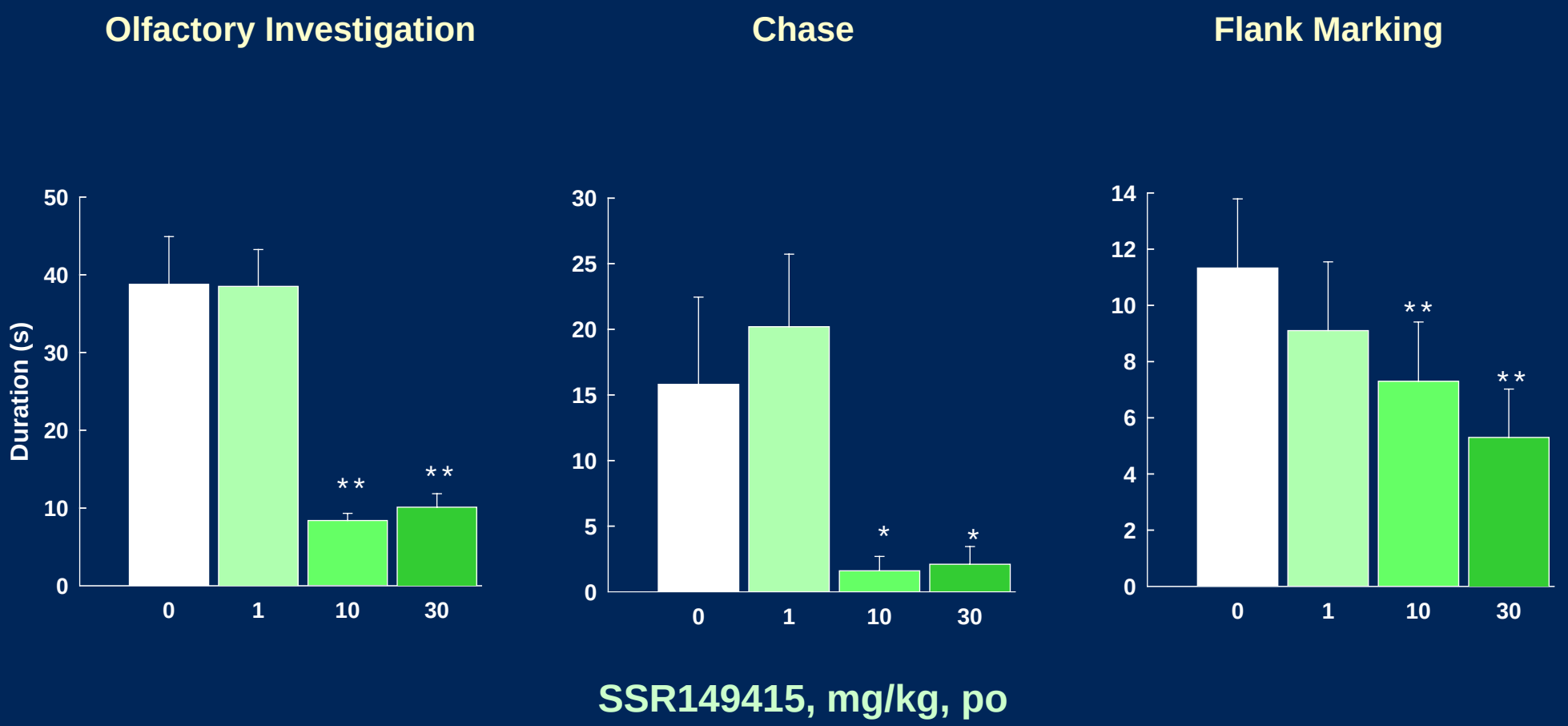
Effects of SSR149415 on offensive aggression in hamsters



SSR149415 reduced both conspecific offensive attack and olfactory investigation in hamsters

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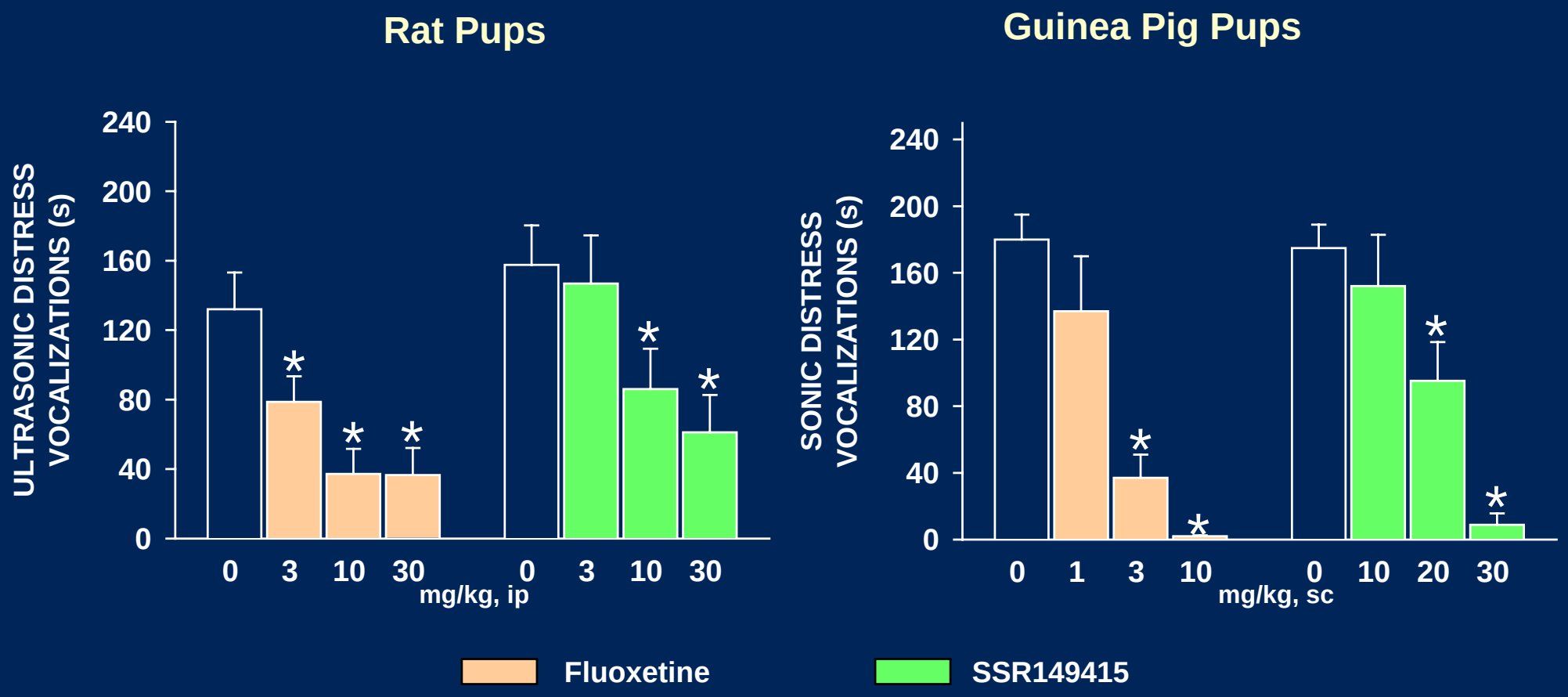
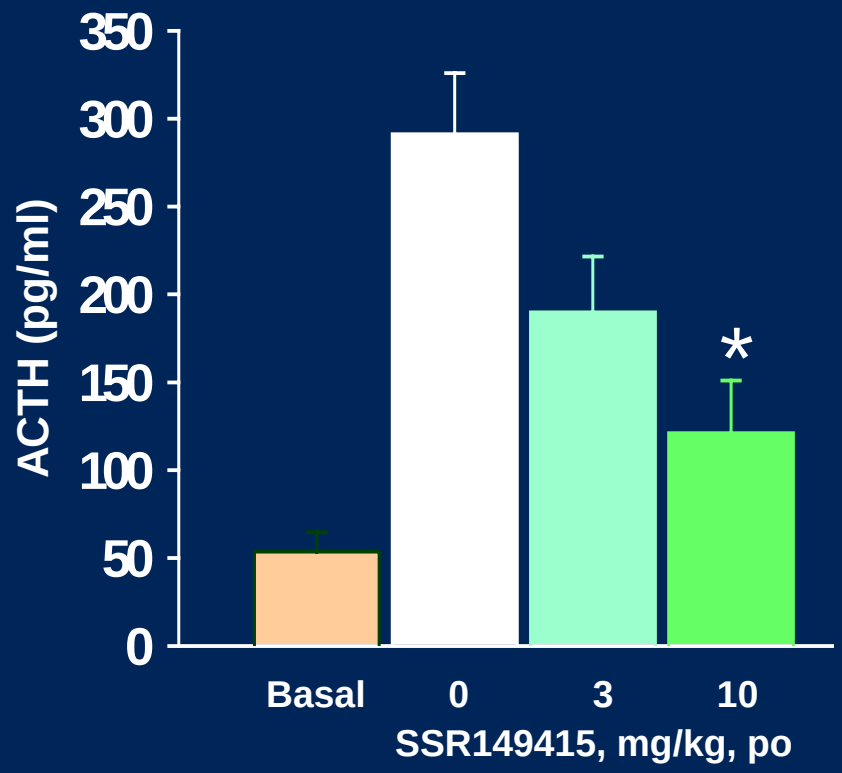
Effects of SSR149415 on maternal separation-induced distress vocalizations in rat or guinea pig pups



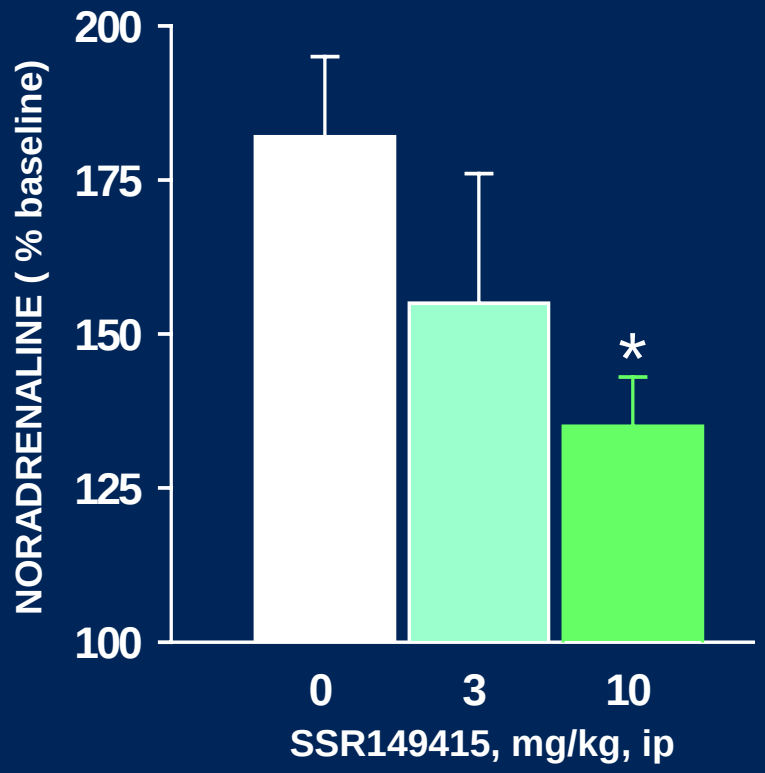
SSR149415 produced a dose-dependent decrease in both sonic and ultrasonic distress vocalizations

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

Restraint Stress-induced increase in plasma ACTH levels



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

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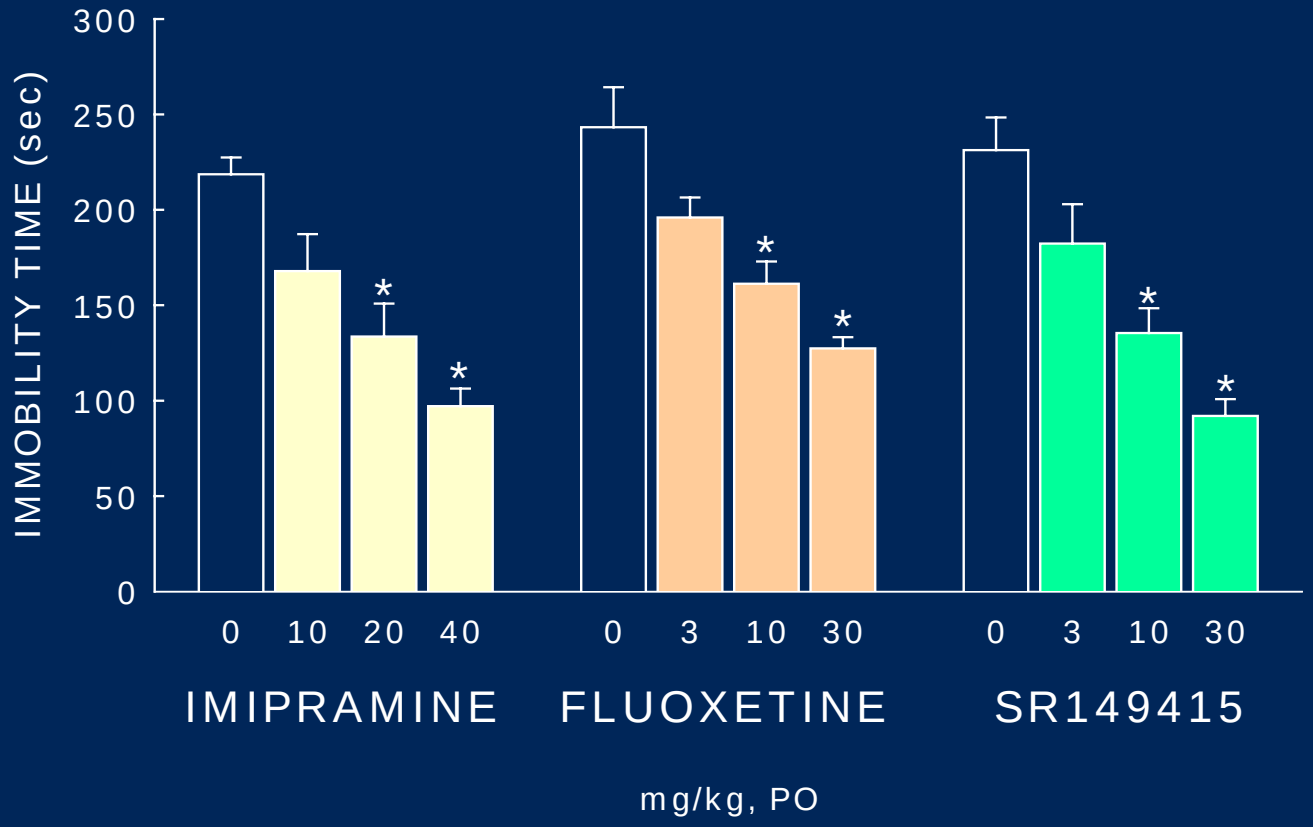
Effects of SSR149415 in an animal model of depression: The forced-swimming test in rats



SSR149415 produced dose-dependent antidepressant-like activity

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The Chronic Mild Stress Procedure in Mice : A model of depression

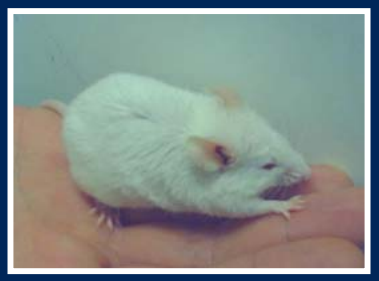
Tests

Treatments

Chronic sequential appplication of mild stressors*

1 2 3 4 5 6 7 8 9 weeks

Non-stressed mouse



Stressed mouse

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

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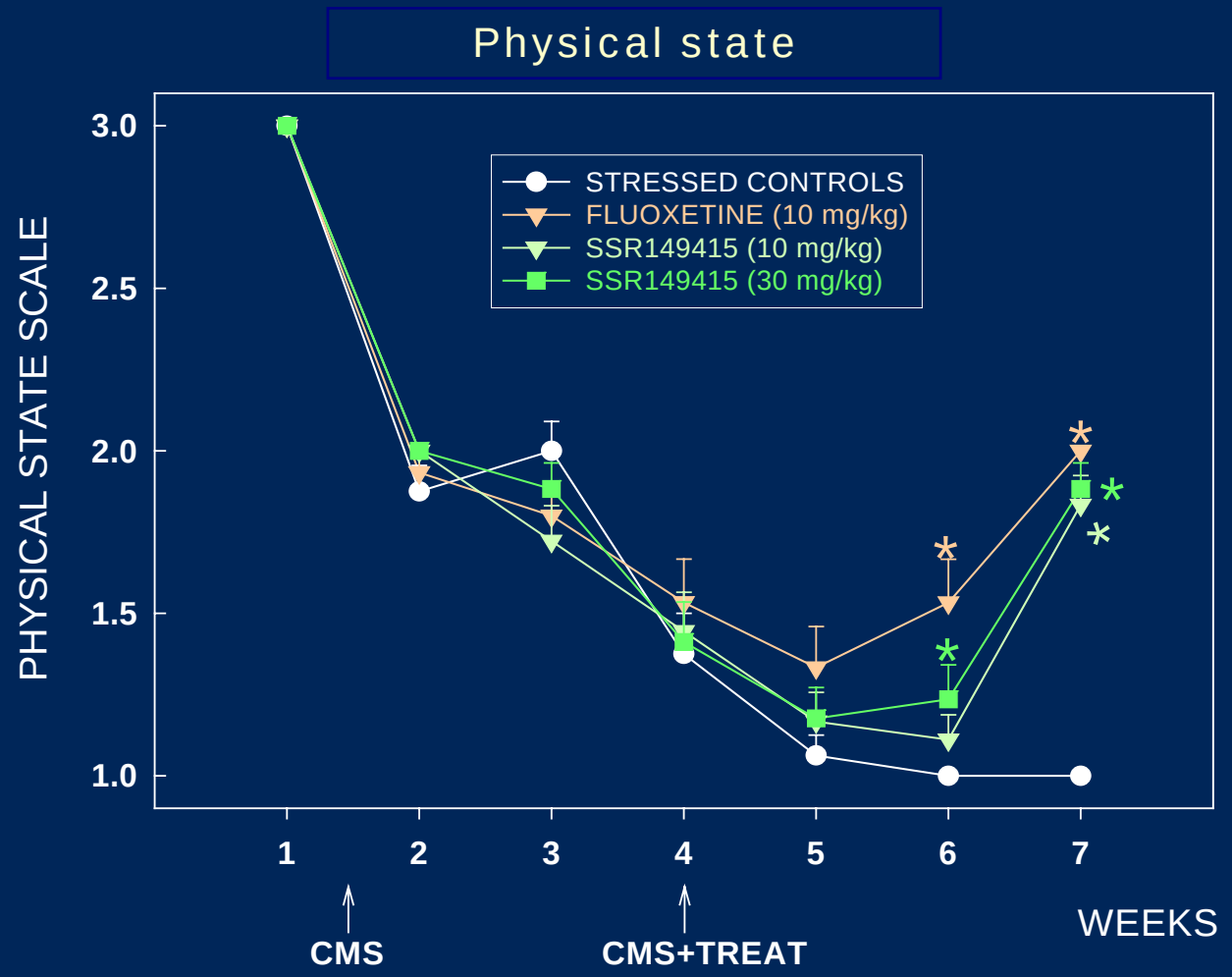
Effects of repeated treatment (39 days/once a day, ip) of SSR149415 in the chronic mild stress model in mice



Repeated administration of SSR149415 reversed the degradation of the physical state produced by stress

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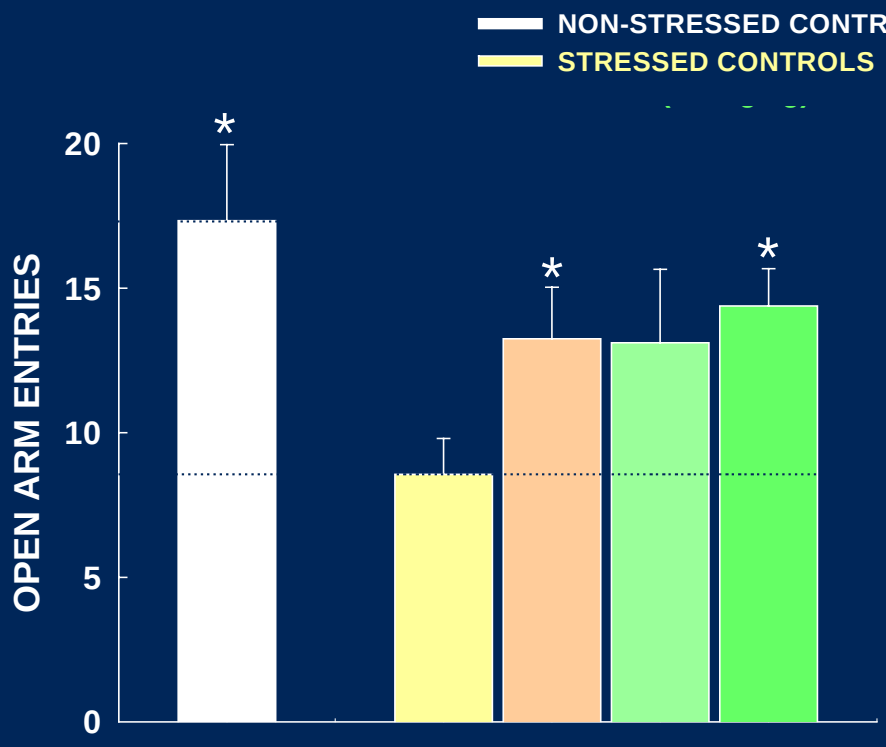
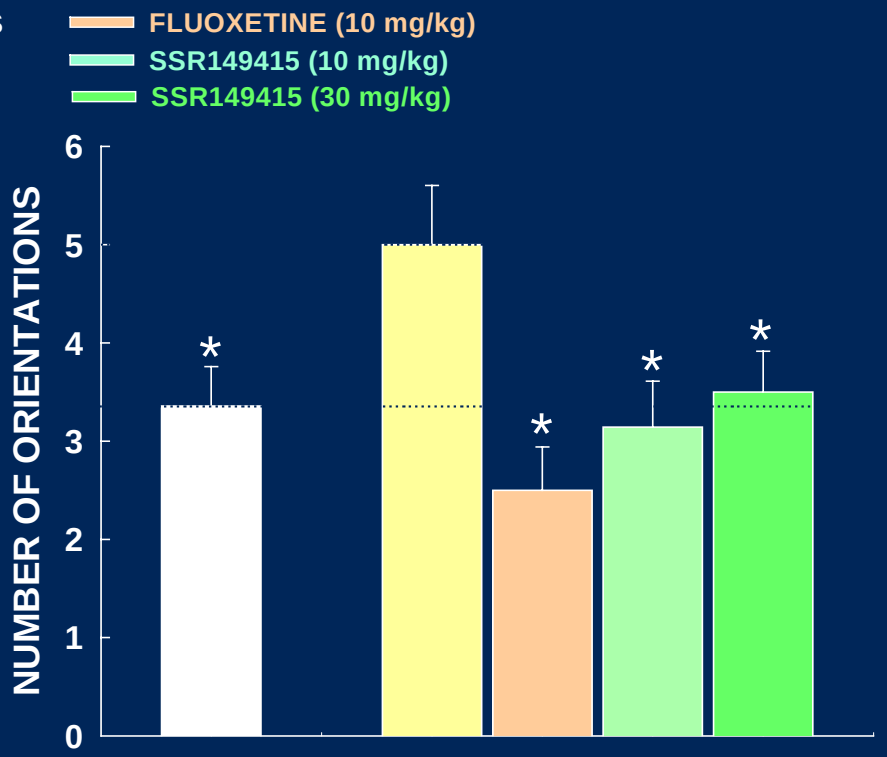
Effects of 39-day treatment (once a day, ip) of SSR149415 in the chronic mild stress model in mice

Anxiety in the Elevated plus-maze

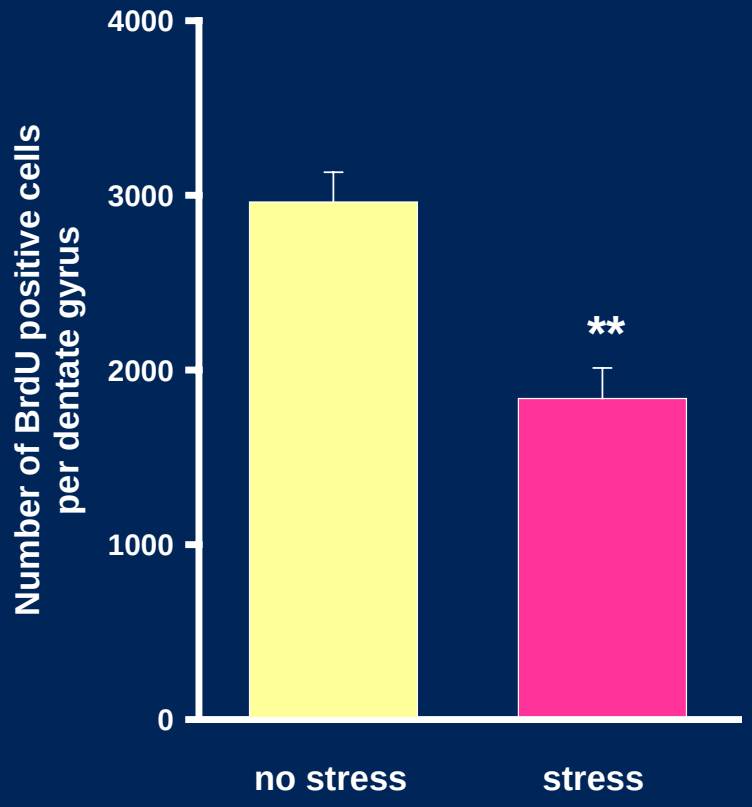


Risk Assessment in the Mouse Defense Test Battery



Repeated administration of SSR149415 reversed anxiety produced by stress

Cell proliferation in the hippocampal dentate gyrus of stressed and non-stressed mice



Chronic mild stress decreases the number of BrdU-positive cells

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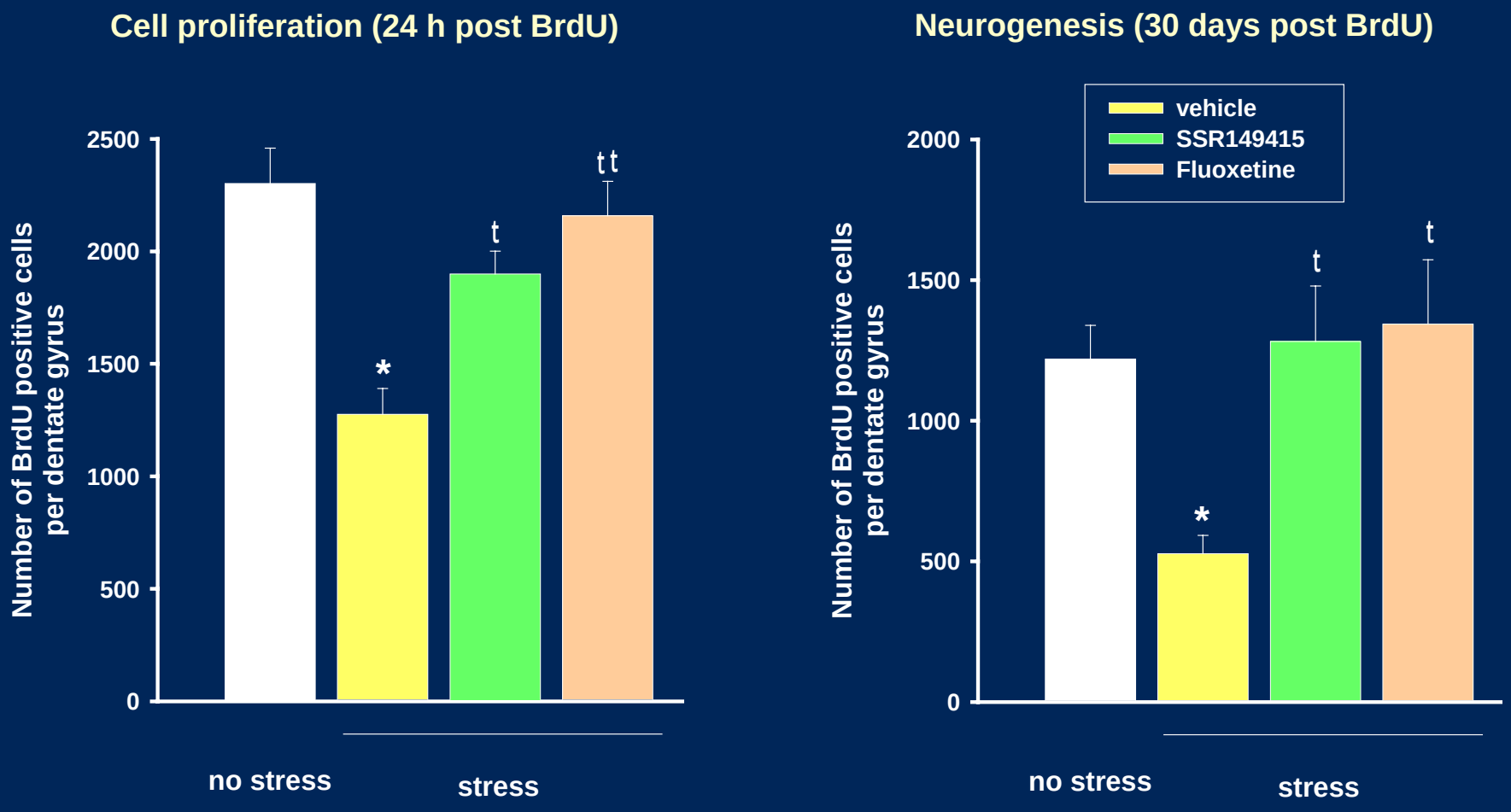
Effect of SSR149415 on chronic mild stress-induced decrease in neurogenesis in the hippocampus of mice



Repeated treatment with SSR149415 prevented stress-induced decrease of cell proliferation in the subgranular zone and neurogenesis in the granular cell layer of the dendate gyrus

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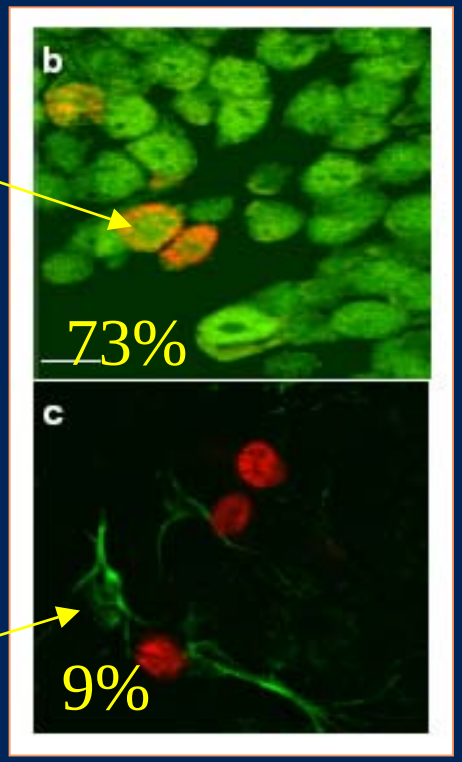
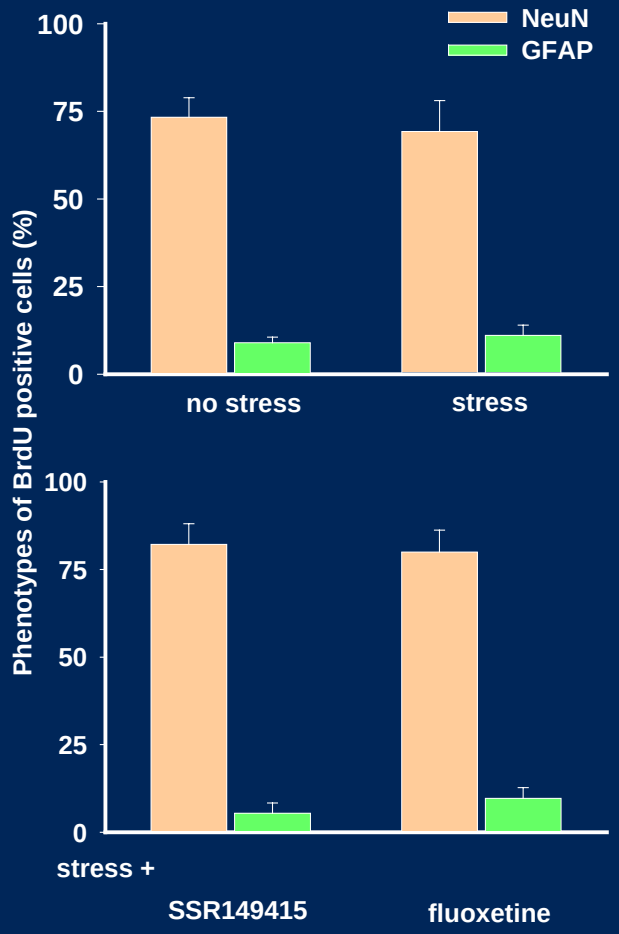
Phenotype of BrdU-labeled cells 30 days after the end of stress exposure

Mature neuron

Glial cells

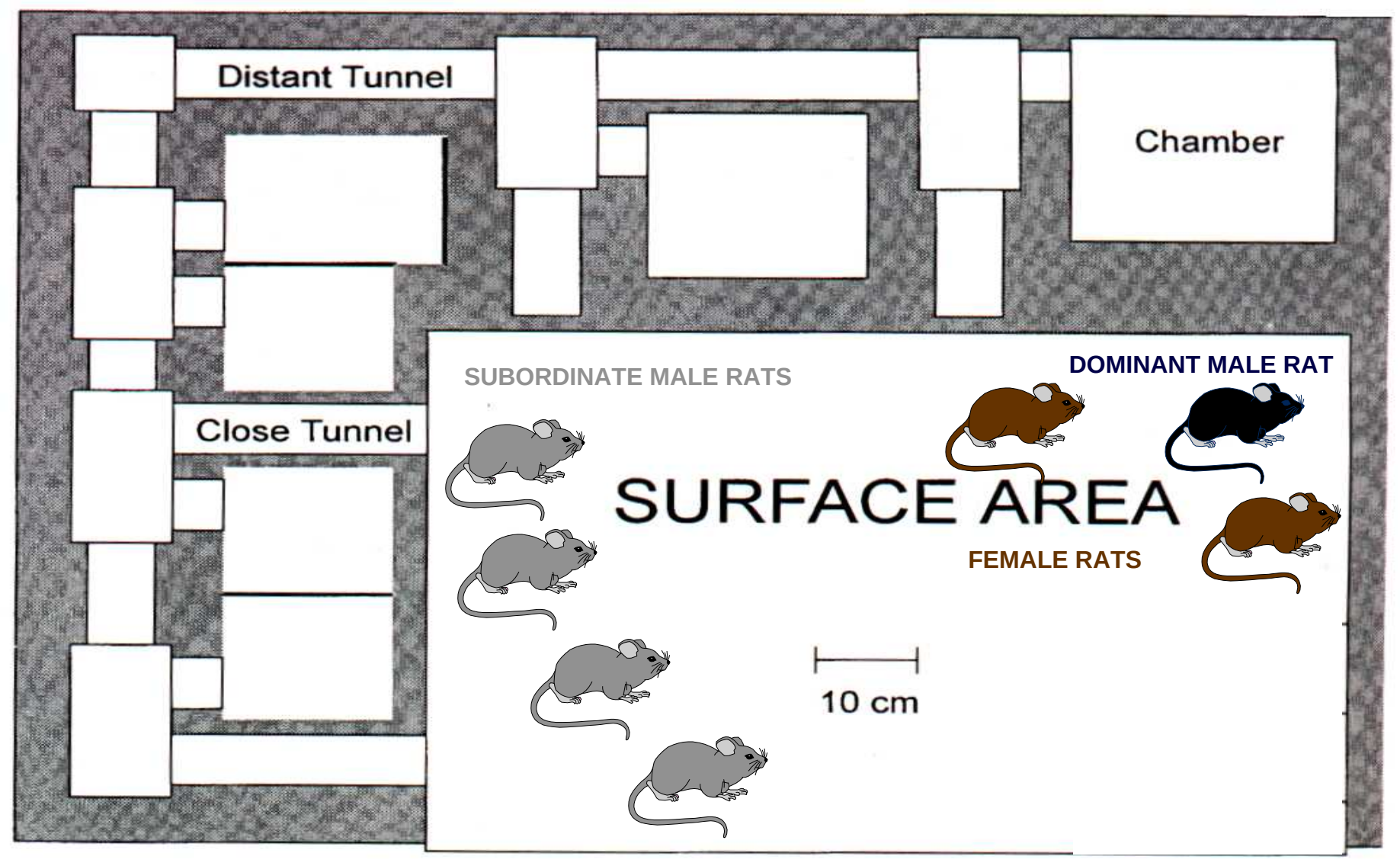




The population of surviving BrdU-positive cells essentially mature into neurons

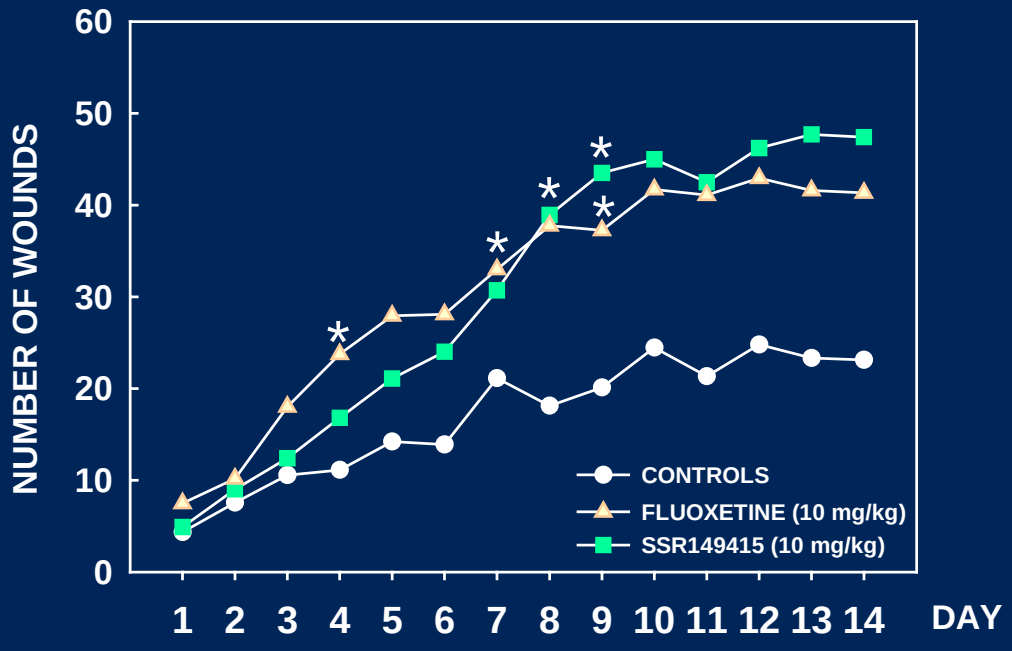
No difference in phenotypic expression patterns between groups

The Visible Burrow System: A Realistic Model of Depression in Rats



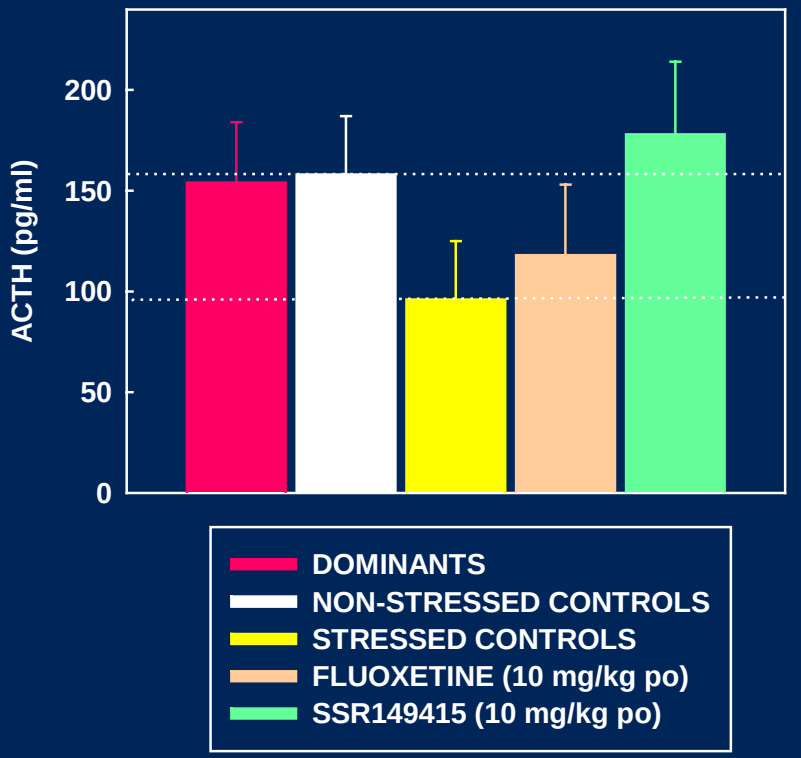
Effects of repeated treatment with SSR149415 on agonistic behavior in socially stressed rats in a visible burrow system

Fighting intensity with the dominant rat



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

ACTH secretion following restraint stress



SSR149415-treated rats showed much higher plasma ACTH levels relative to vehicle subordinates, suggesting normalization of this HPA axis parameter

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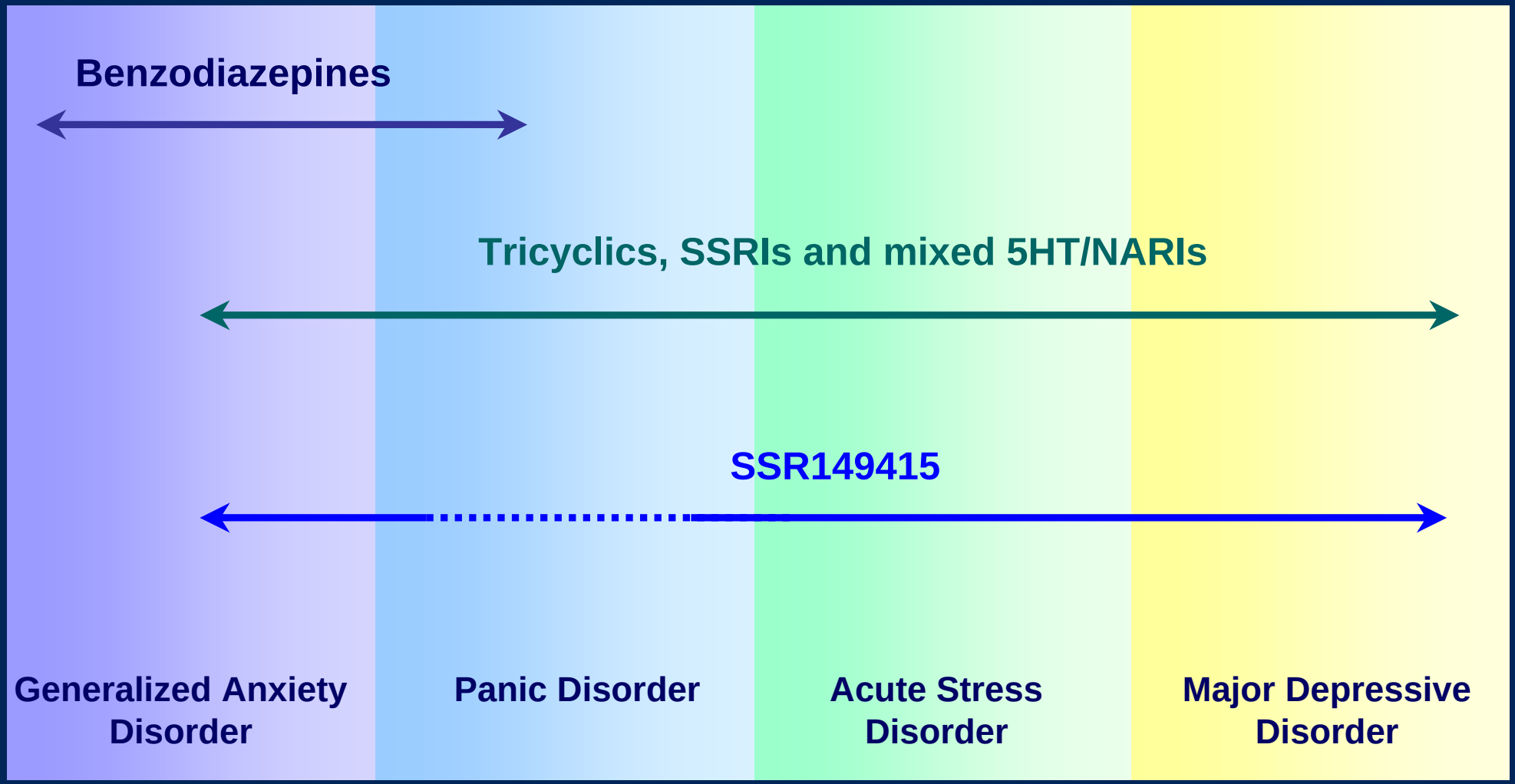
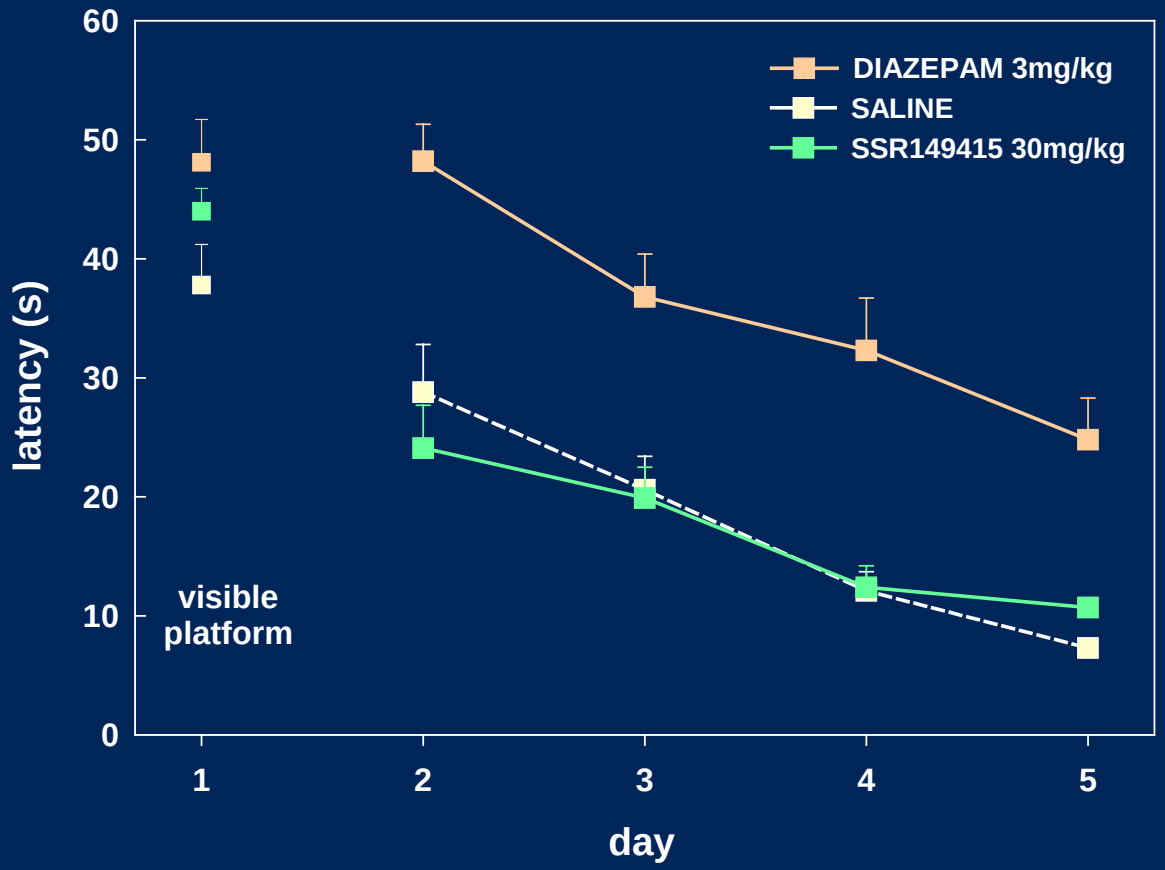
Expected clinical spectrum of therapeutic activity of SSR149415 in anxiety / depressive disorders



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.

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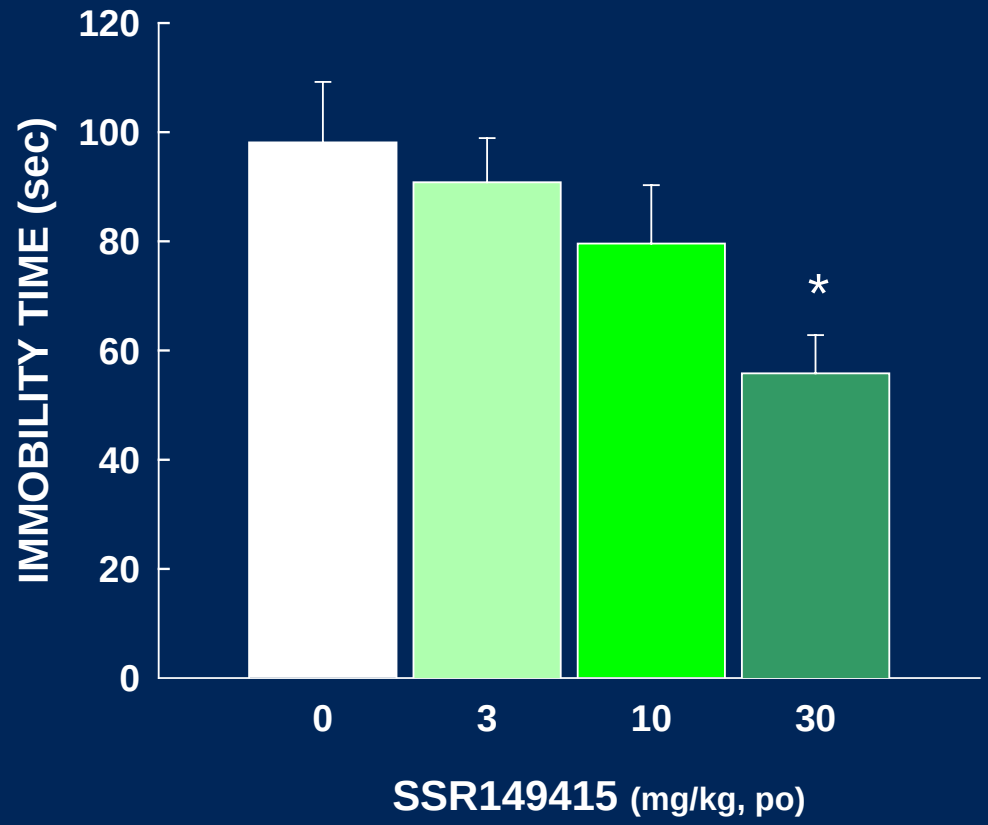
Effects of SSR149415 in the forced-swimming test in hypophysectomized rats



SSR149415 is still effective in hypophysectomized rats, indicating that the antidepressant-like effects do not depend on blocking only the hypothalamic V_{1b} receptors

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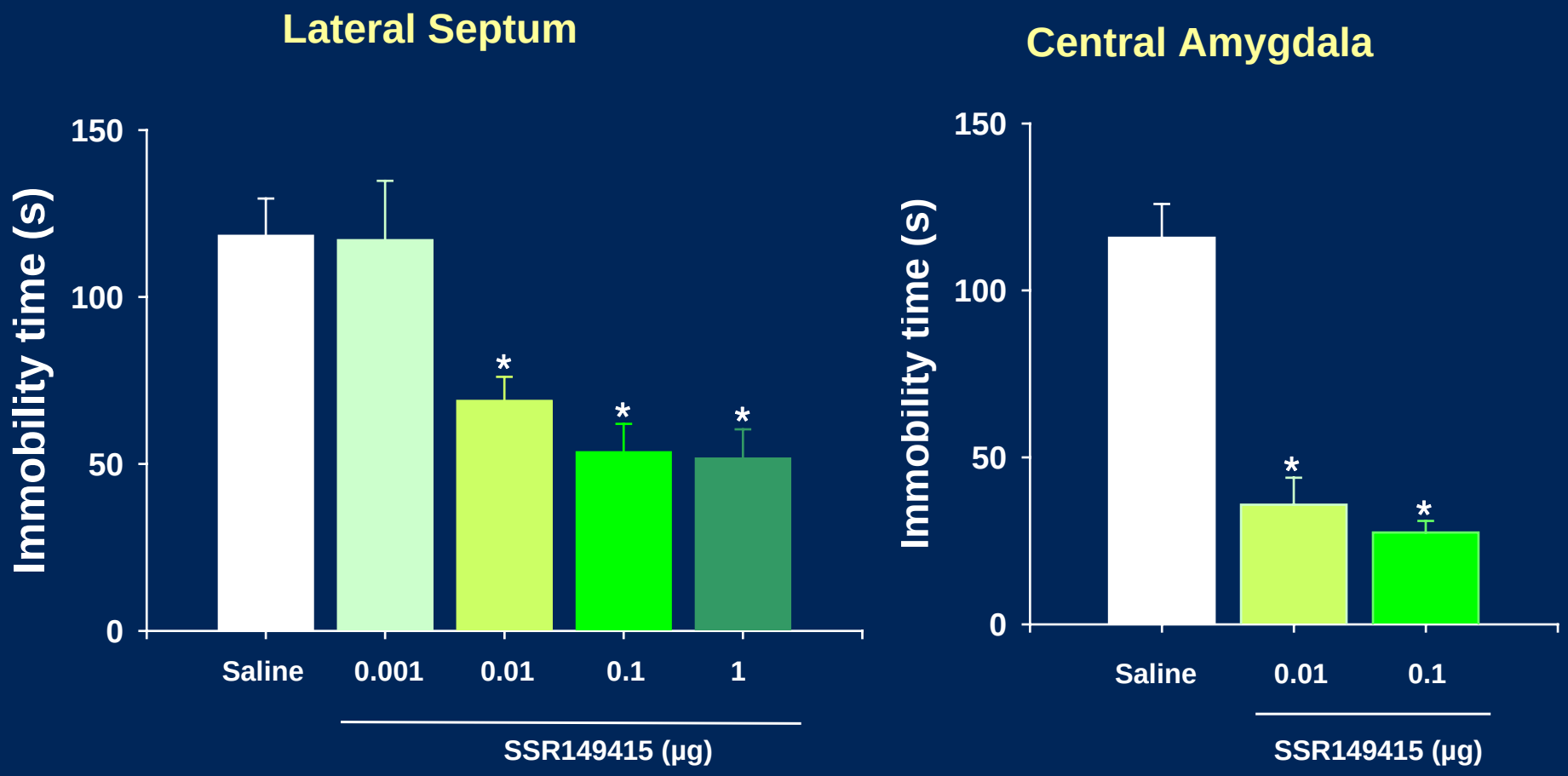
Effects of local infusions of SSR149415 in the forced-swimming test in rats



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

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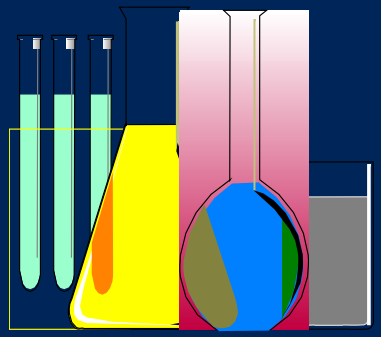
Conclusion

- 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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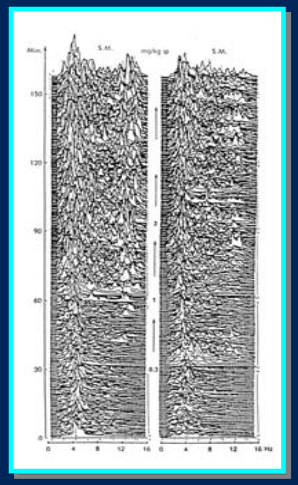

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