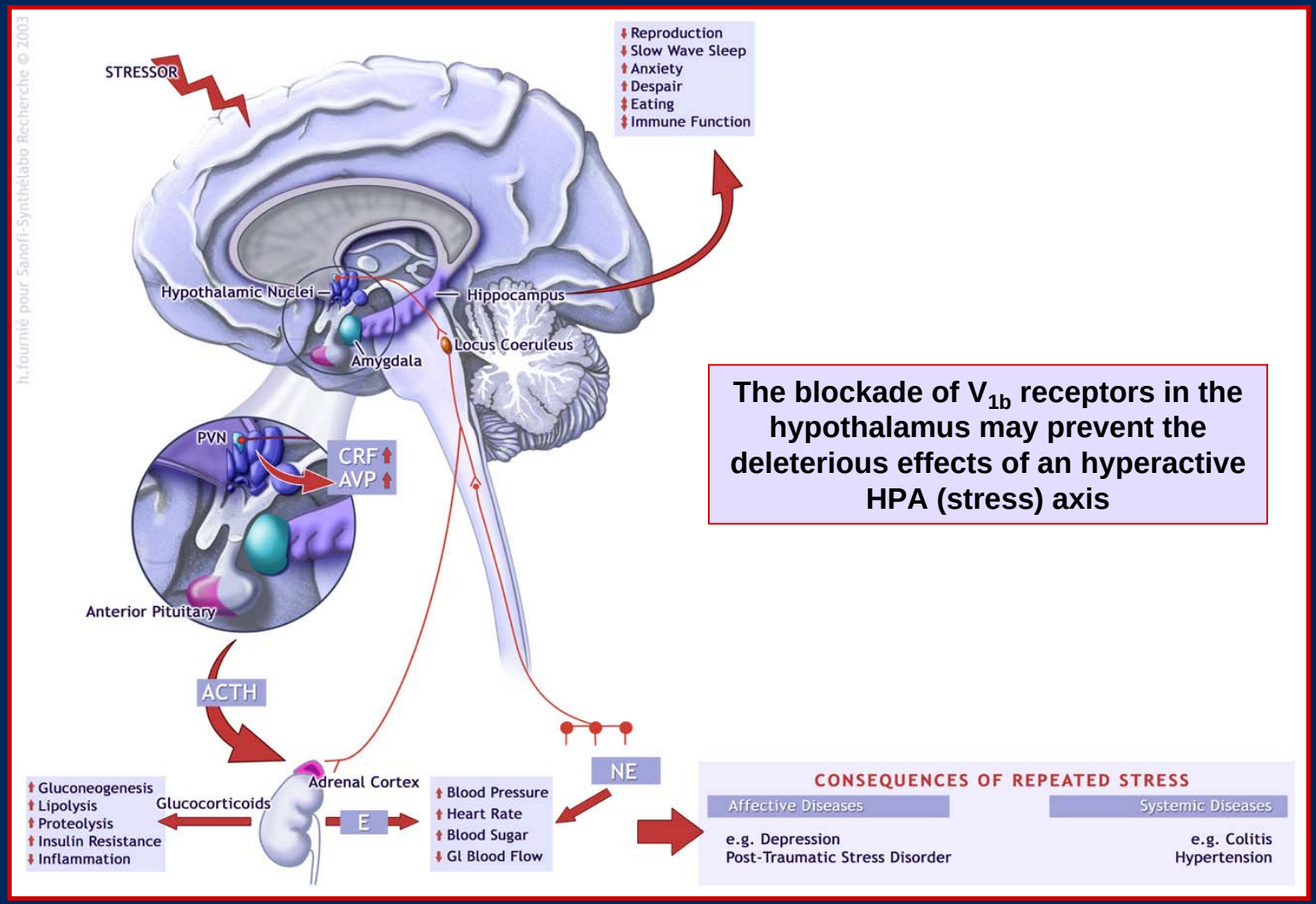
The Vasopressin V_{1b} Receptor as a Therapeutic Target in Stress-Related Disorders

Guy Griebel

Second Joint French – Swiss Meeting on Medicinal Chemistry
Beaune, 1-4 July 2003

sanofi~synthelabo

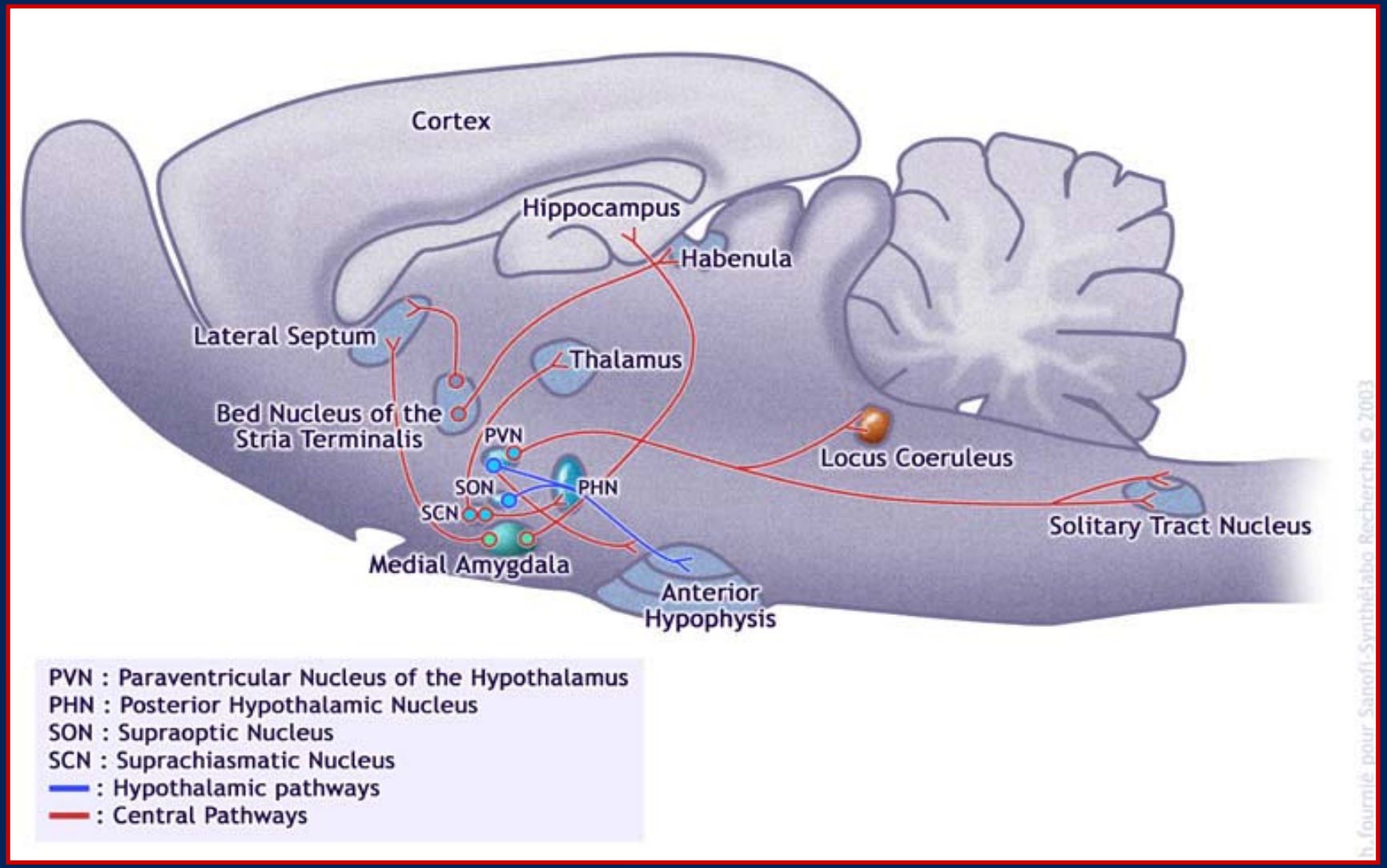
Schematic representation of the endocrine, behavioral and autonomic responses to stress mediated by vasopressin (AVP), and the consequences of repeated stress



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

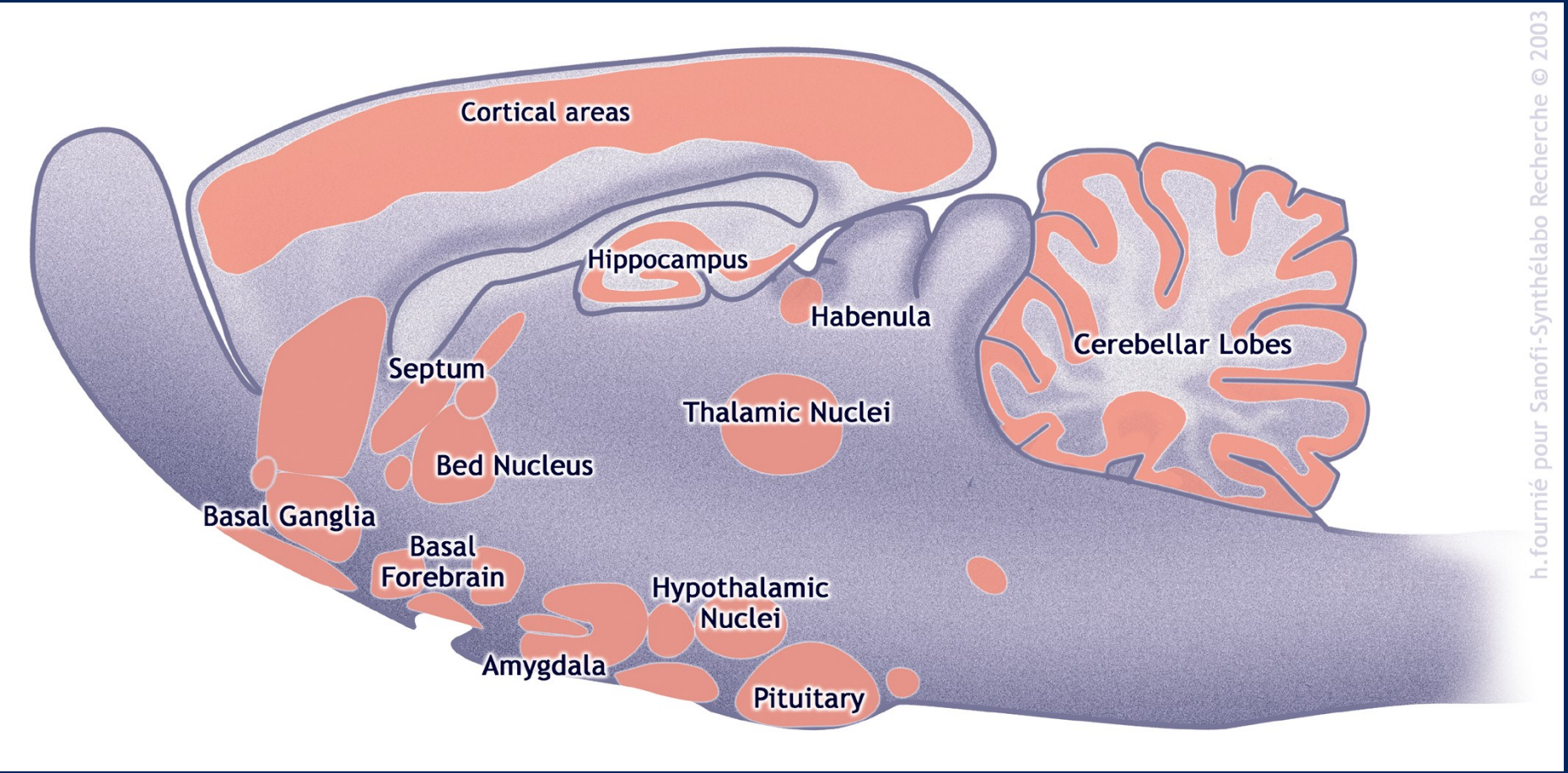
sanofi~synthelabo

The vasopressin pathways in the brain



sanofi~synthelabo

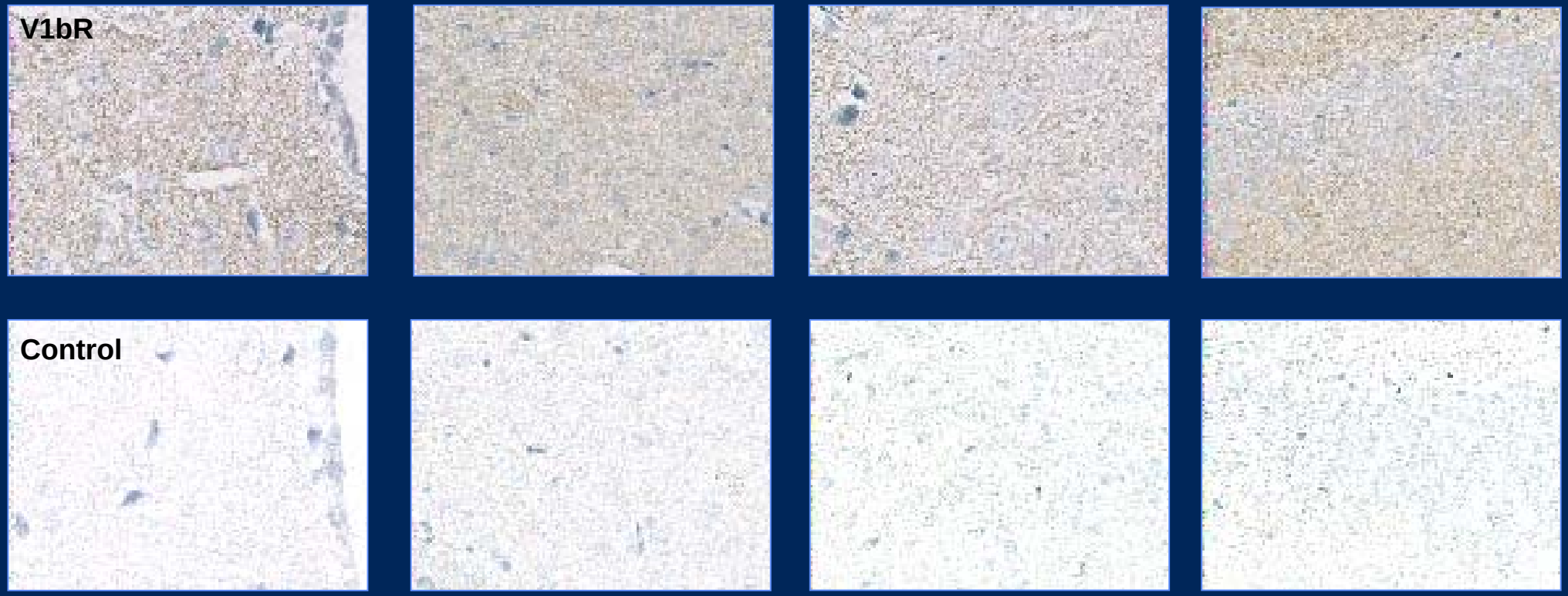
Immunohistochemical localization of the V_{1b} receptor in the rat brain



sanofi~synthelabo

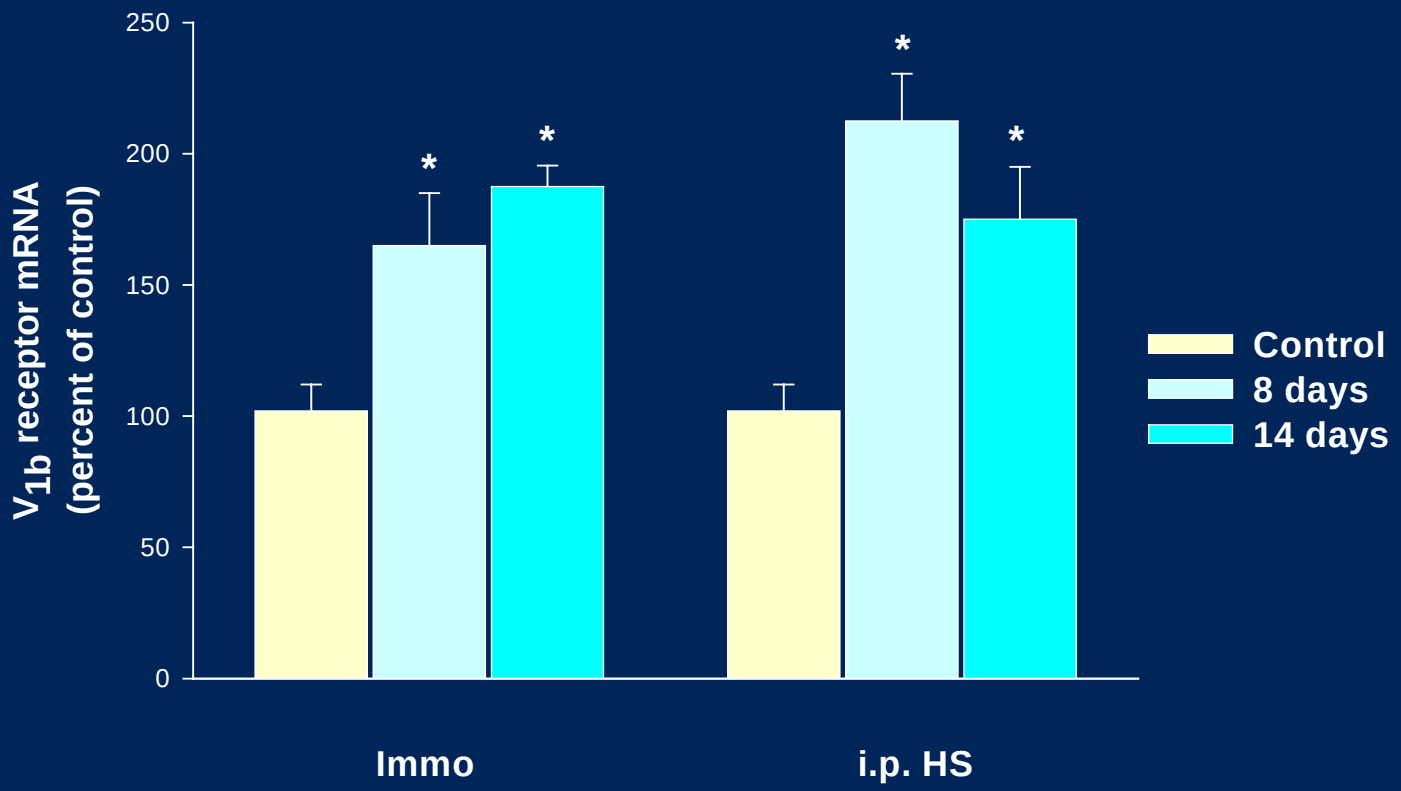
Immunohistochemical localization of V_{1b} receptors in brain areas known to modulate anxiety behaviors in rats

Lateral Septum	Bed Nucleus of the Stria Terminalis	Amygdala	Dendate Gyrus



sanofi~synthelabo

The V_{1b} receptor and stress

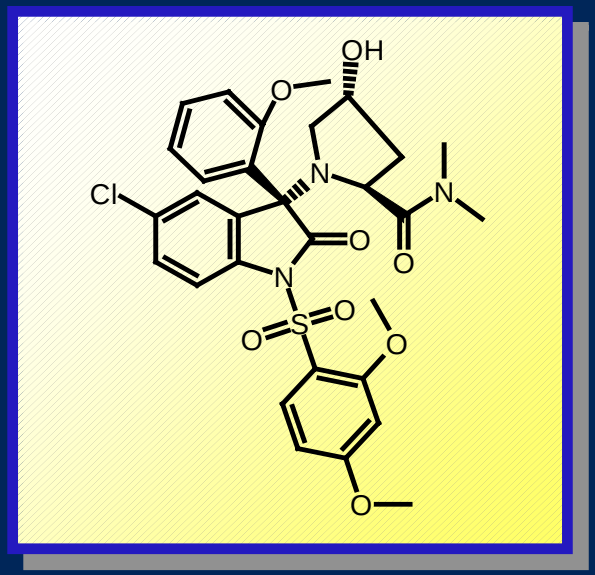


Rabadan-Diehl et al., J. Neuroendocrinol. 7 : 903-10, 1995

Eight or 14 days immobilization stress or hypertonic saline injection (ip HS) increases V_{1b} receptor mRNA

sanofi~synthelabo

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(-)**

sanofi~synthelabo

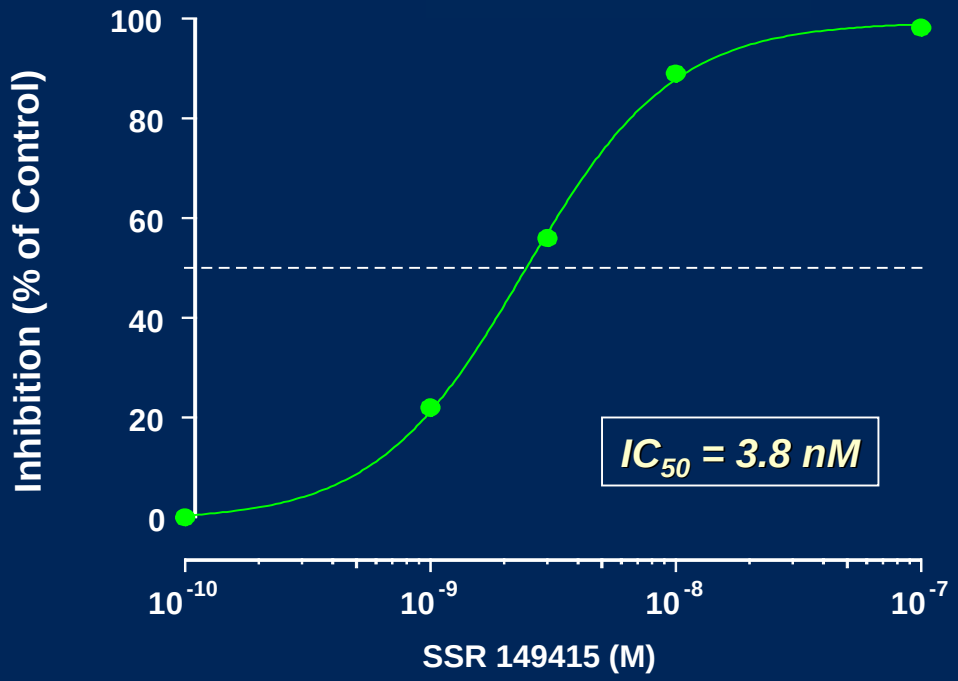
Selectivity profile of SSR149415 for vasopressin and oxytocin receptors

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

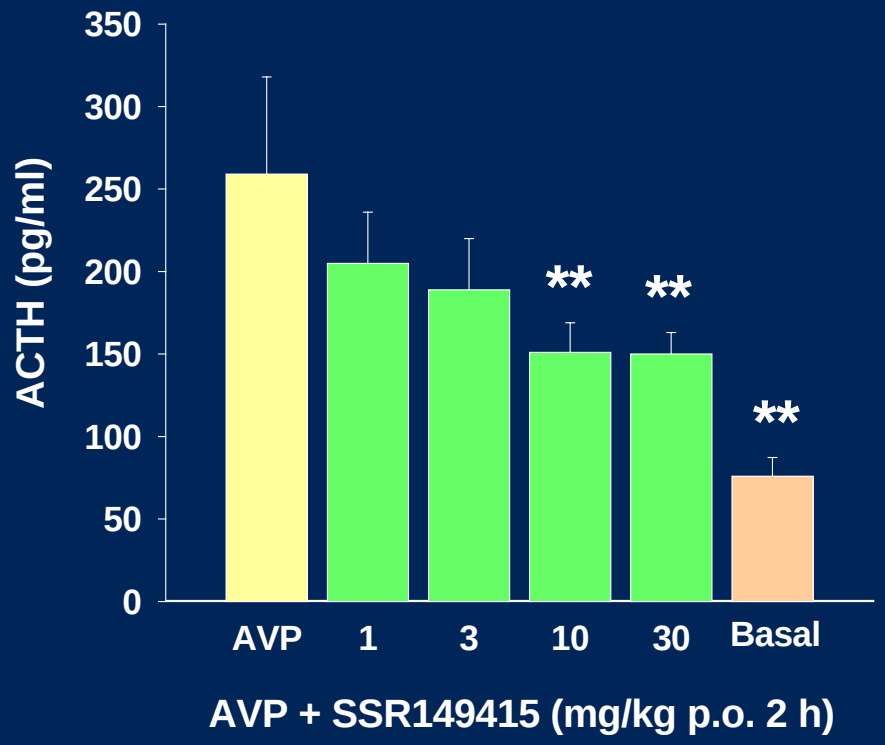
Inhibition by SSR149415 of AVP-induced Ca^{2+} increase in CHO cells transfected with the human V_{1b} receptor.



SSR149415 is a competitive antagonist

sanofi~synthelabo

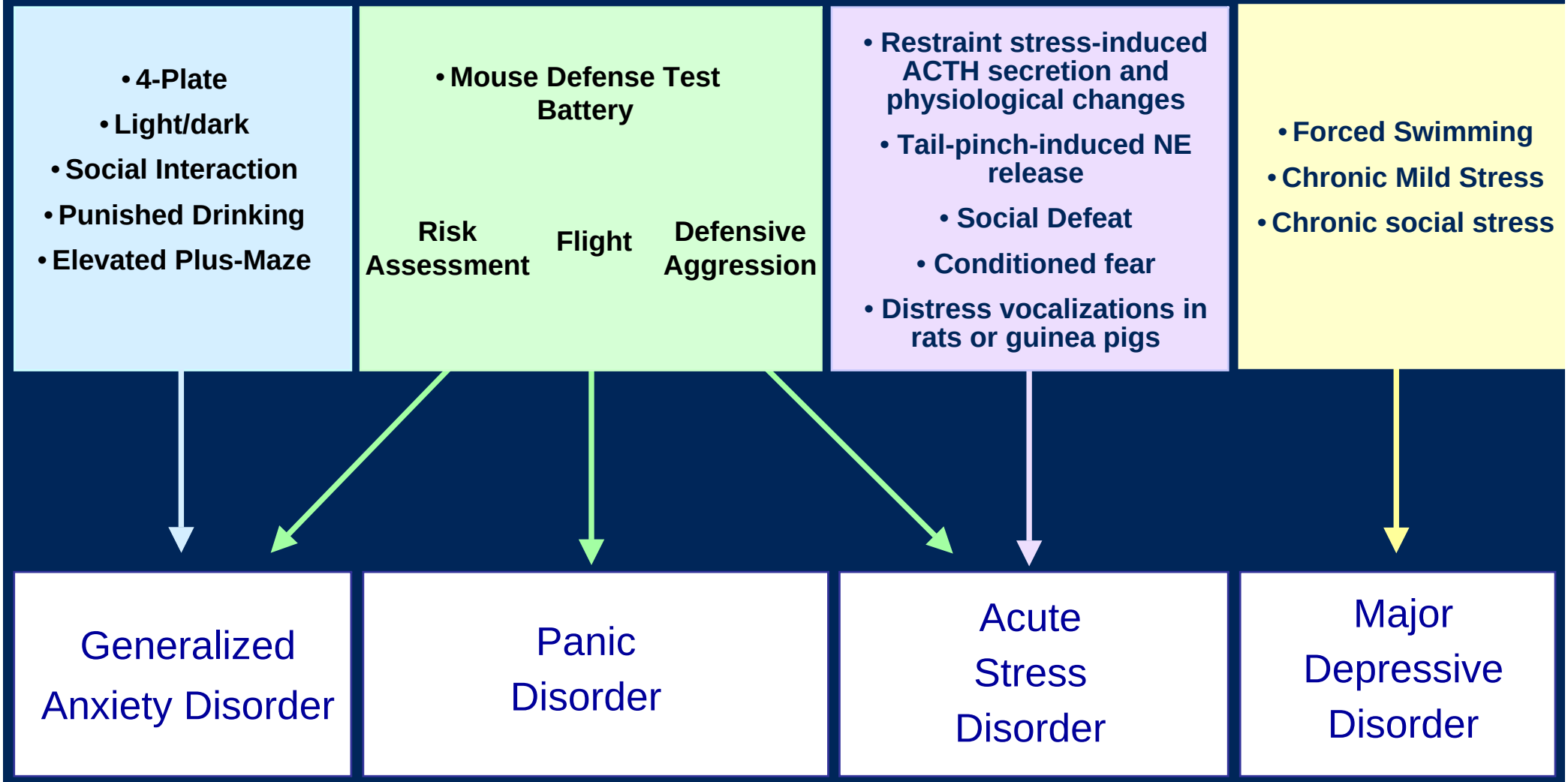
Effects of SSR149415 on vasopressin-induced ACTH secretion in conscious rats



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

sanofi~synthelabo

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

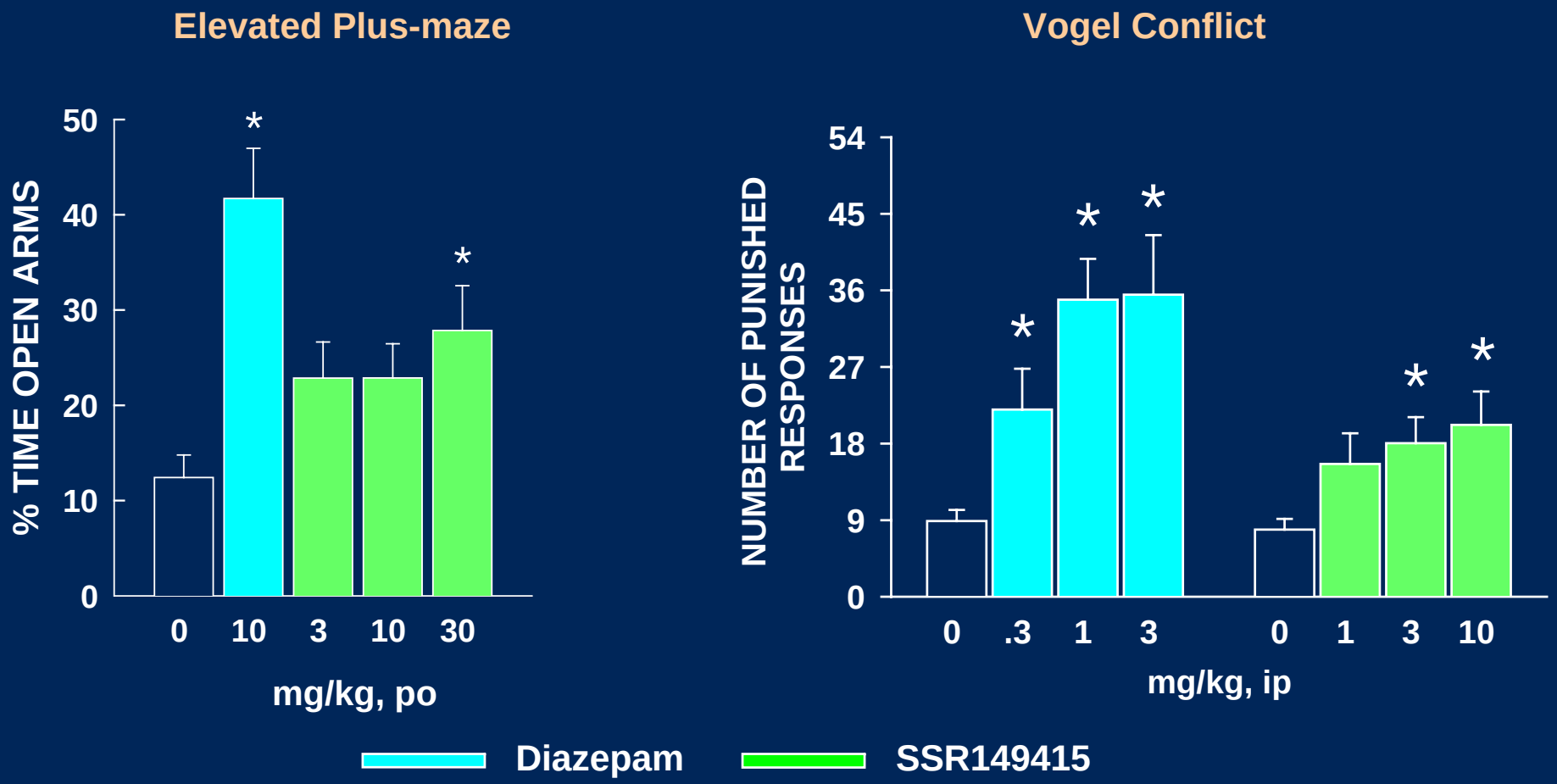


*According to the DSM-IV classification (1994)

Second Joint French – Swiss Meeting on Medicinal Chemistry
Beaune, 1-4 July 2003

sanofi~synthelabo

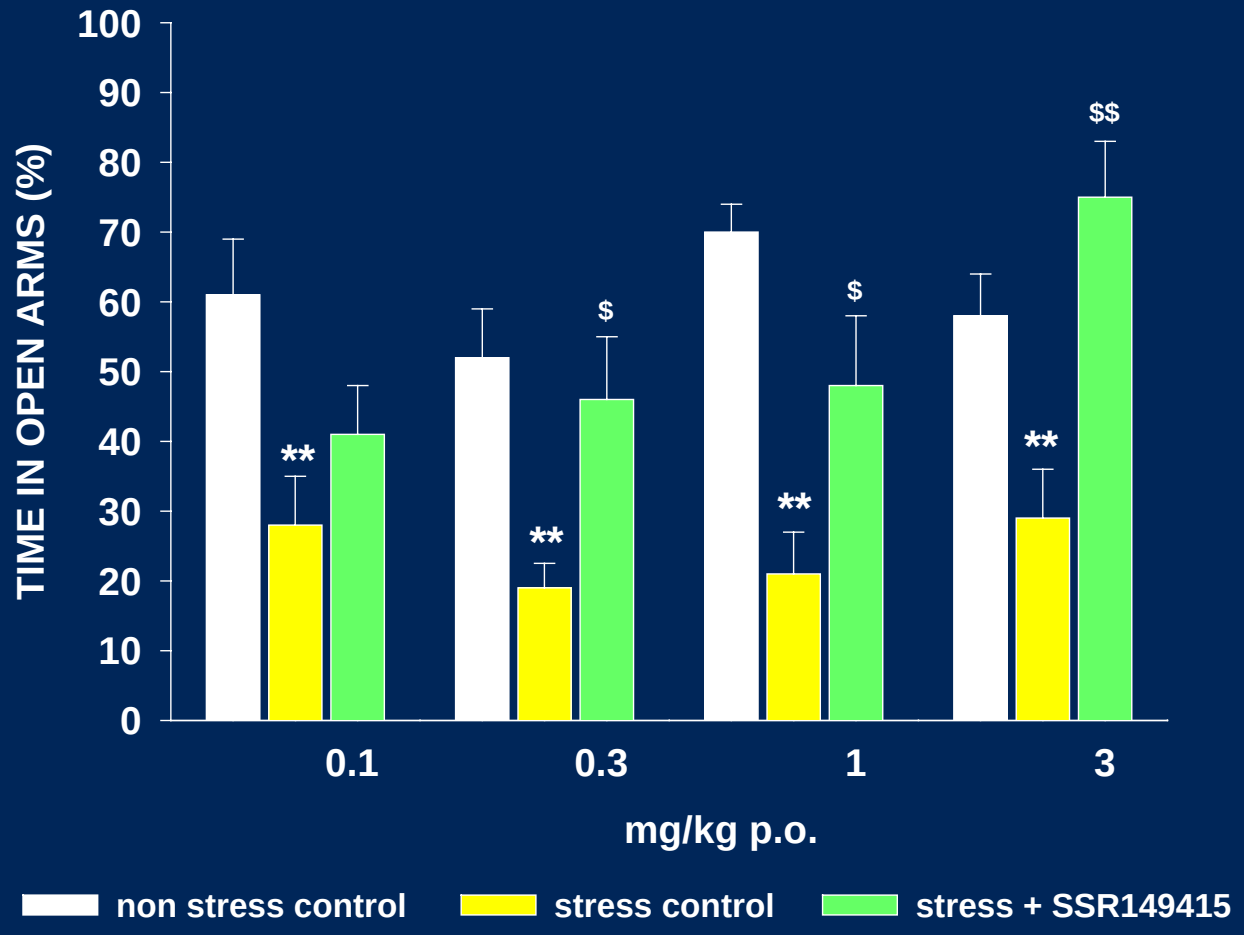
Effects of SSR149415 in two classical models of anxiety: The elevated plus-maze and Vogel conflict tests in rats



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

sanofi~synthelabo

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

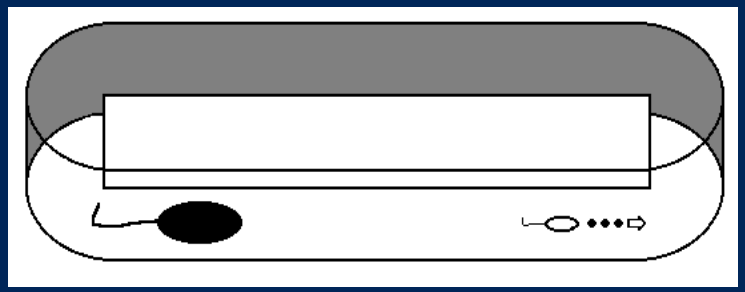


SSR149415 antagonized the heightened emotionality in the elevated plus-maze produced by prior (stressful) exposure to an aggressive isolated resident

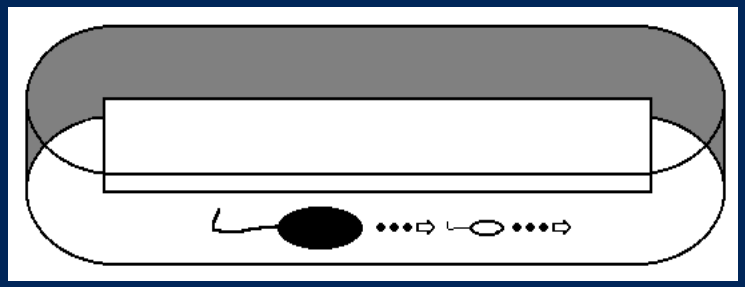
sanofi~synthelabo

The mouse defense test battery

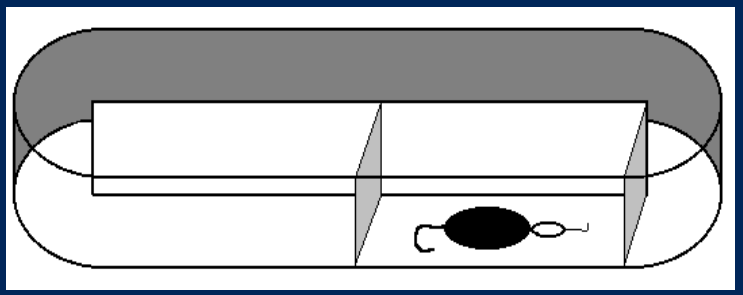
FLIGHT →



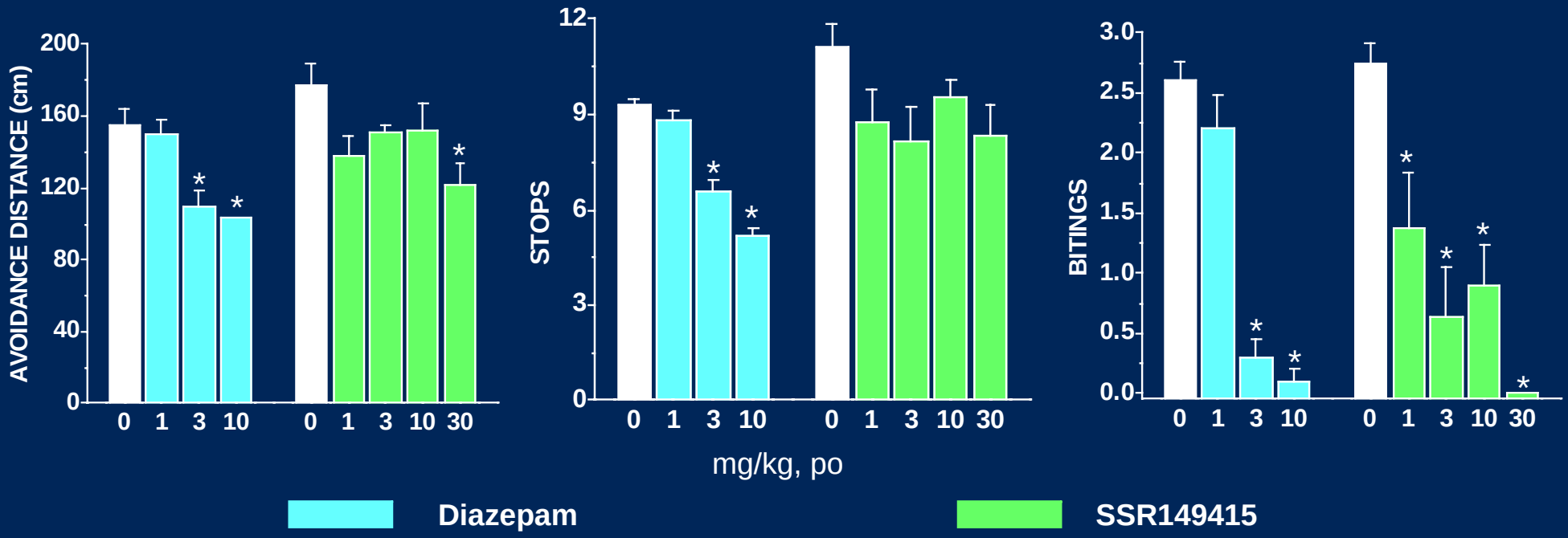
RISK ASSESSMENT →



DEFENSIVE AGGRESSION →



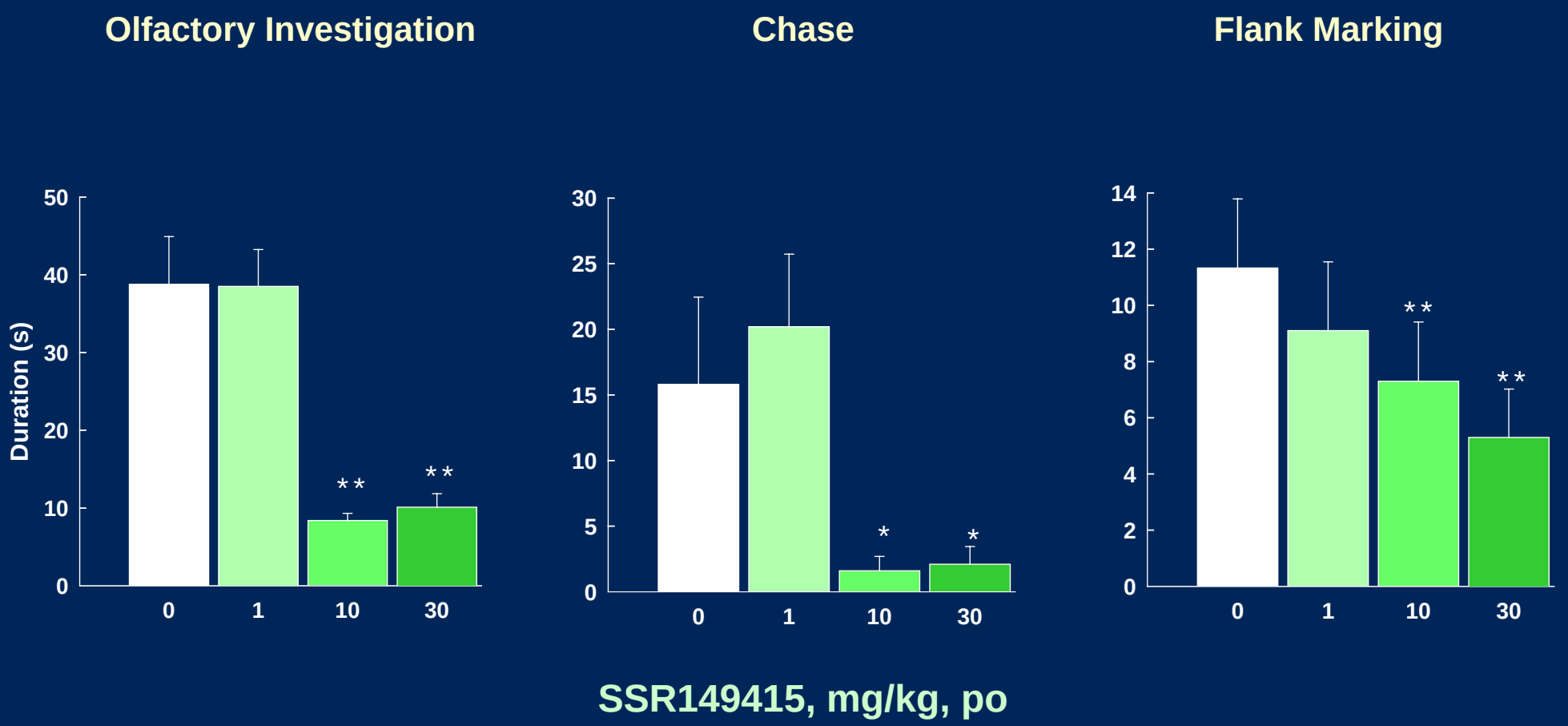
Effects of SSR149415 in the mouse defense test battery



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

sanofi~synthelabo

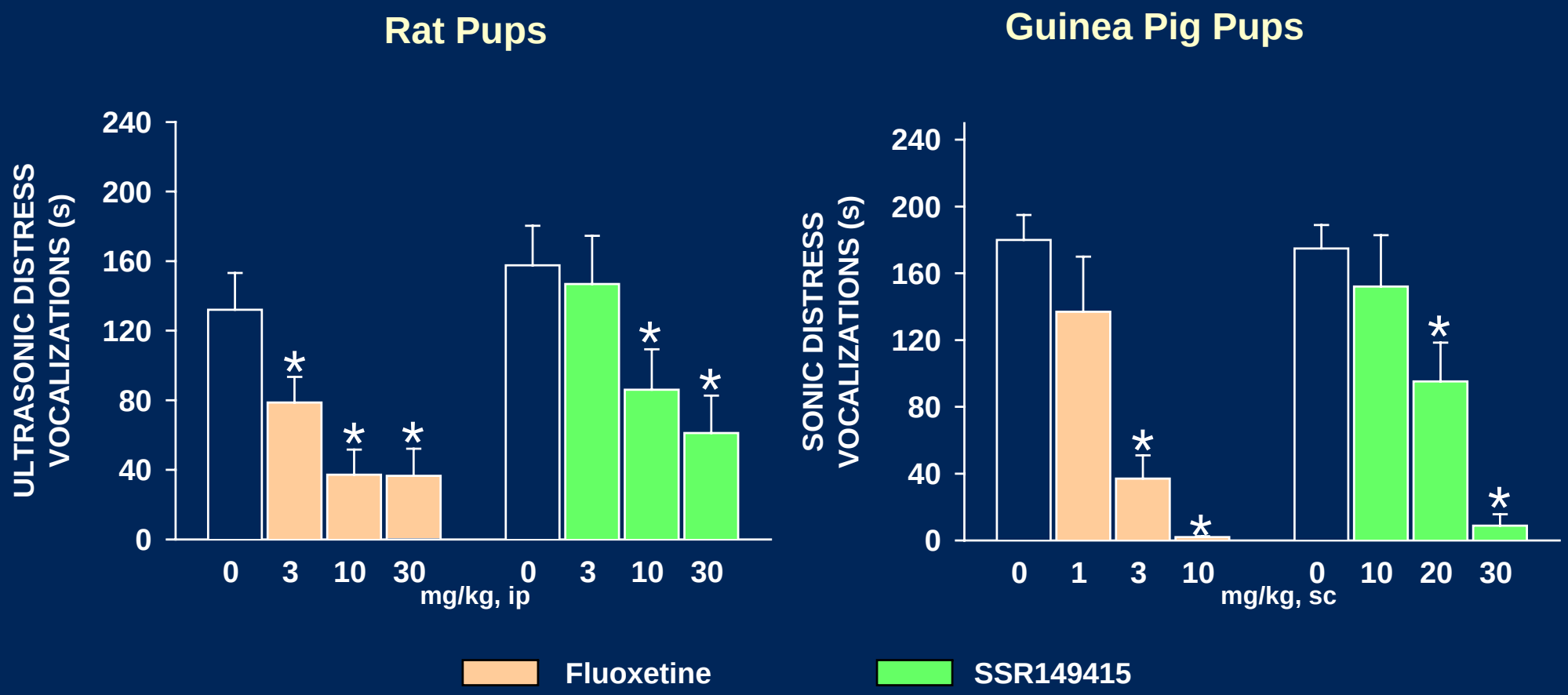
Effects of SSR149415 on offensive aggression in hamsters



SSR149415 reduced both conspecific offensive attack and olfactory investigation in hamsters

sanofi~synthelabo

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

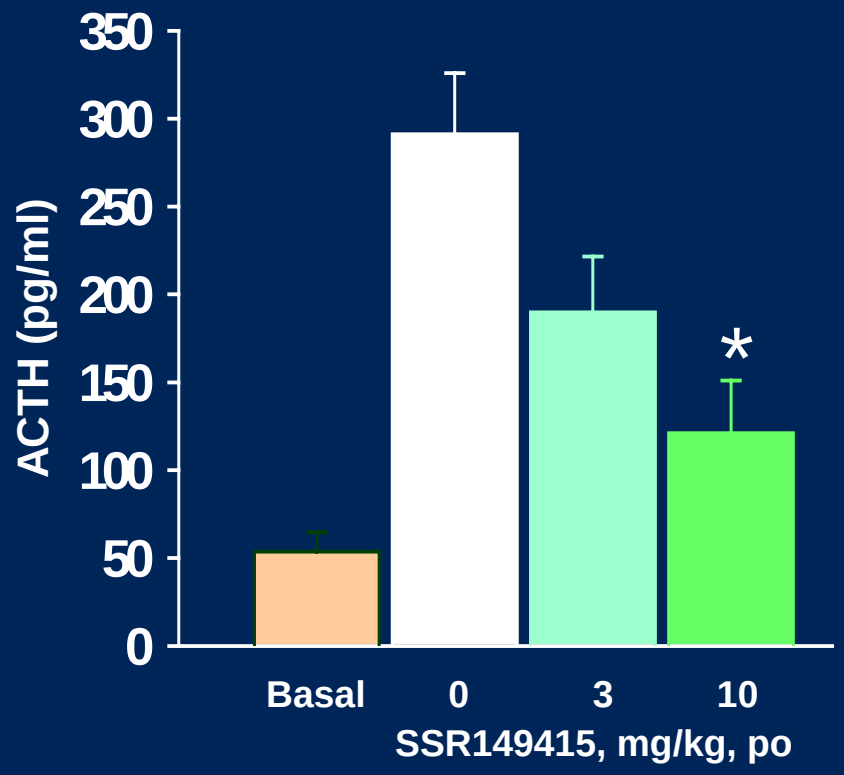


SSR149415 produced a dose-dependent decrease in both sonic and ultrasonic distress vocalizations

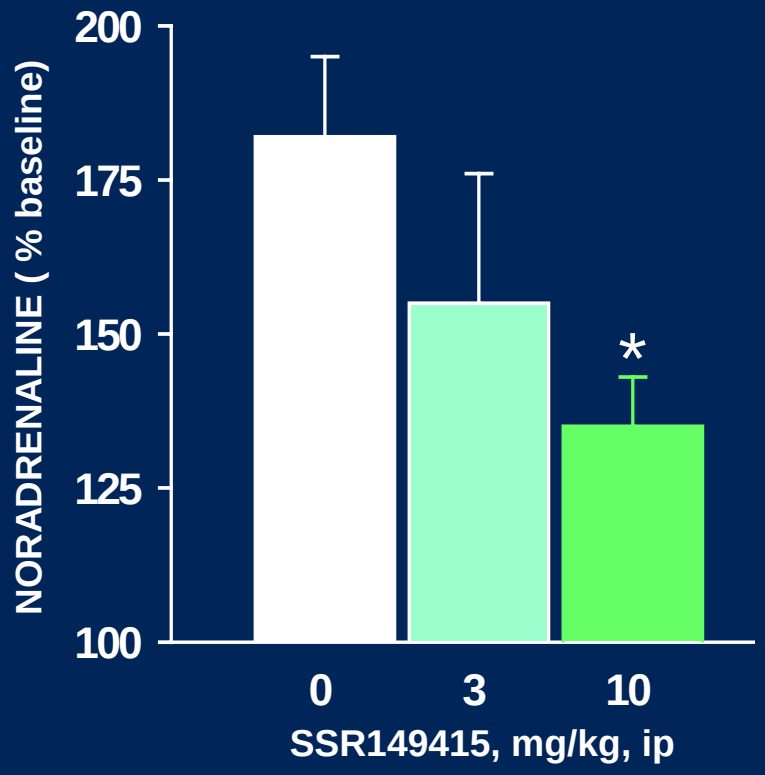
sanofi~synthelabo

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

Restraint Stress-induced increase in plasma ACTH levels



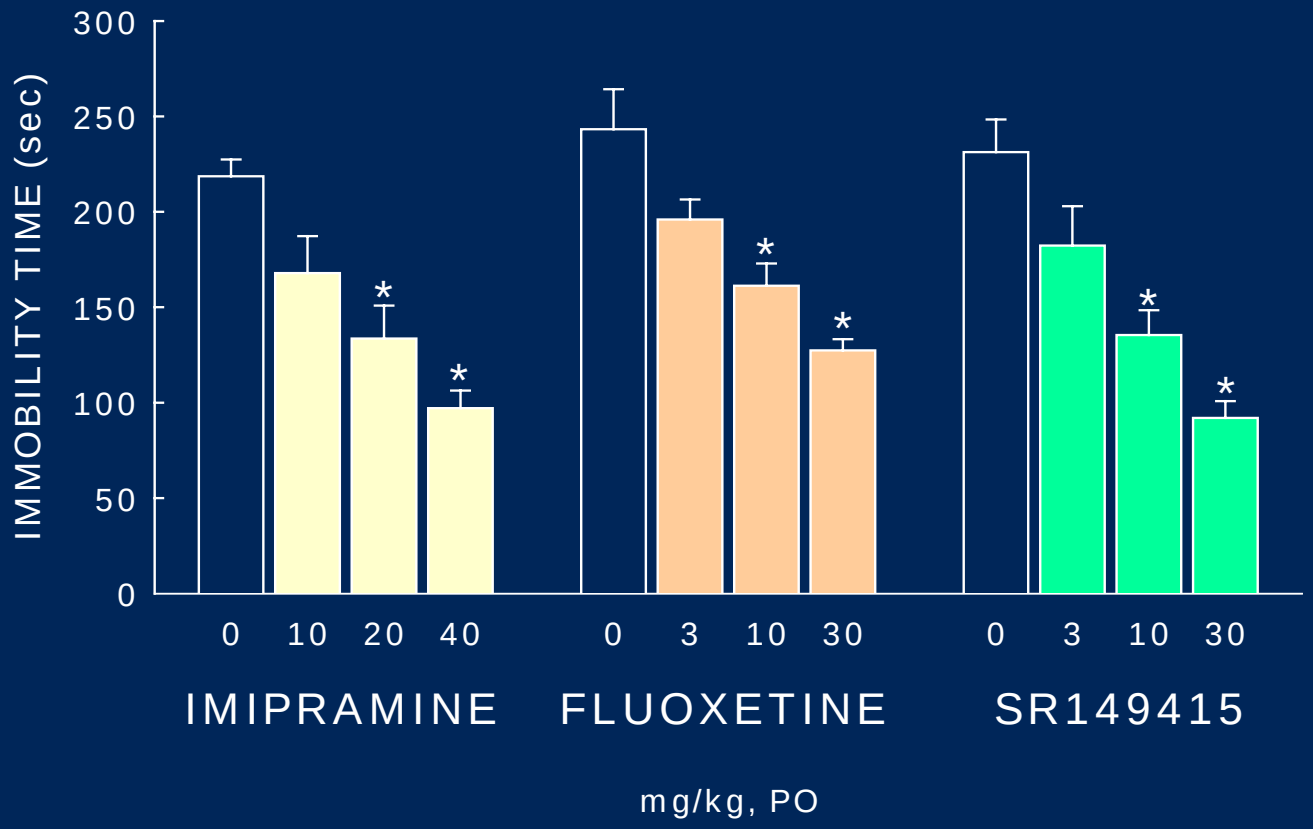
Tail Pinch Stress-induced release in NE in the prefrontal cortex



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

sanofi~synthelabo

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



SSR149415 produced dose-dependent antidepressant-like activity

sanofi~synthelabo

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

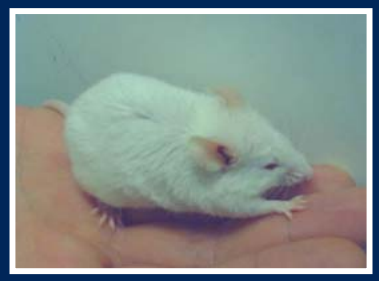
Tests

Treatments

Chronic sequential appplication of mild stressors*

1 2 3 4 5 6 7 8 9 weeks

Non-stressed mouse

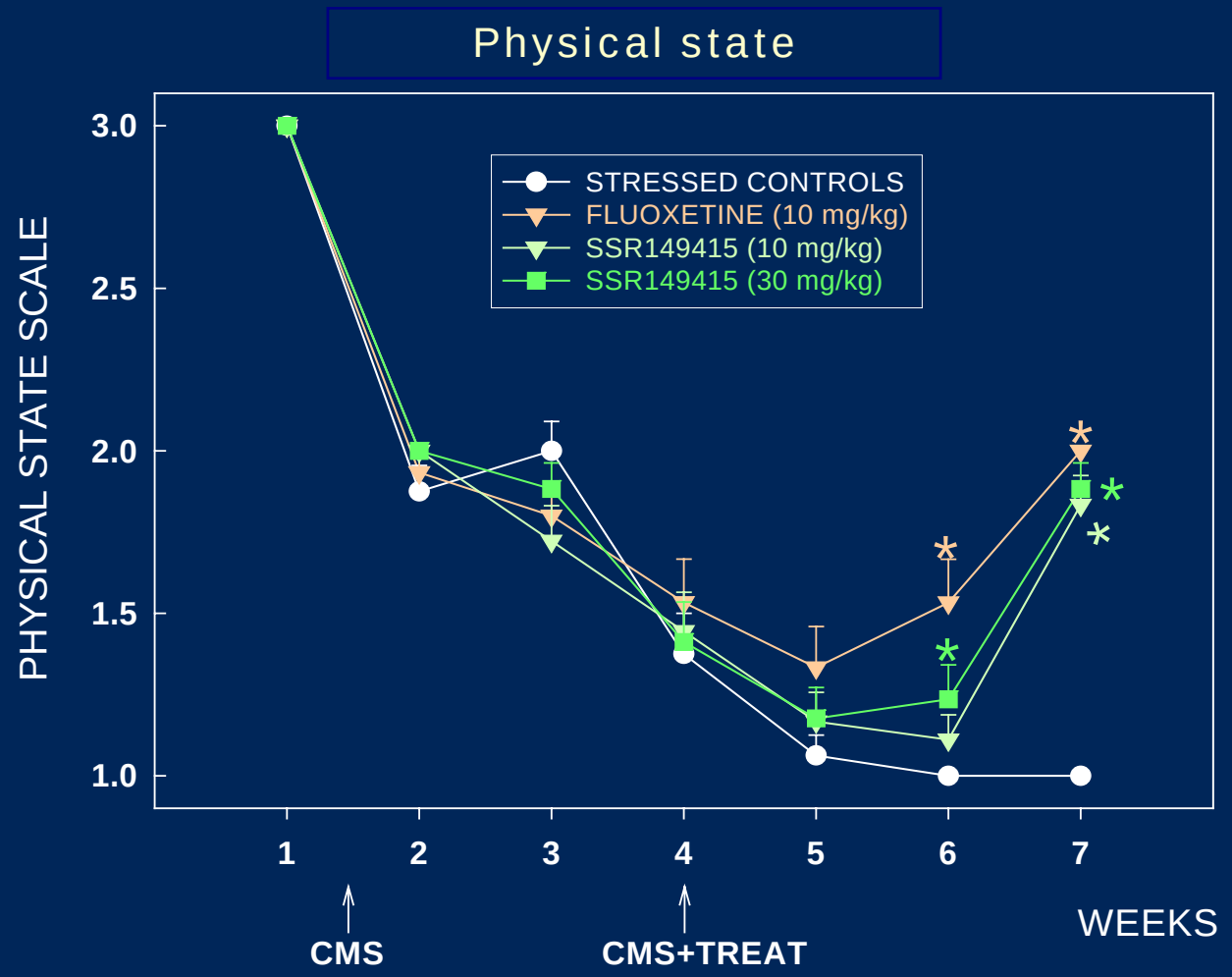


Stressed mouse

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

sanofi~synthelabo

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

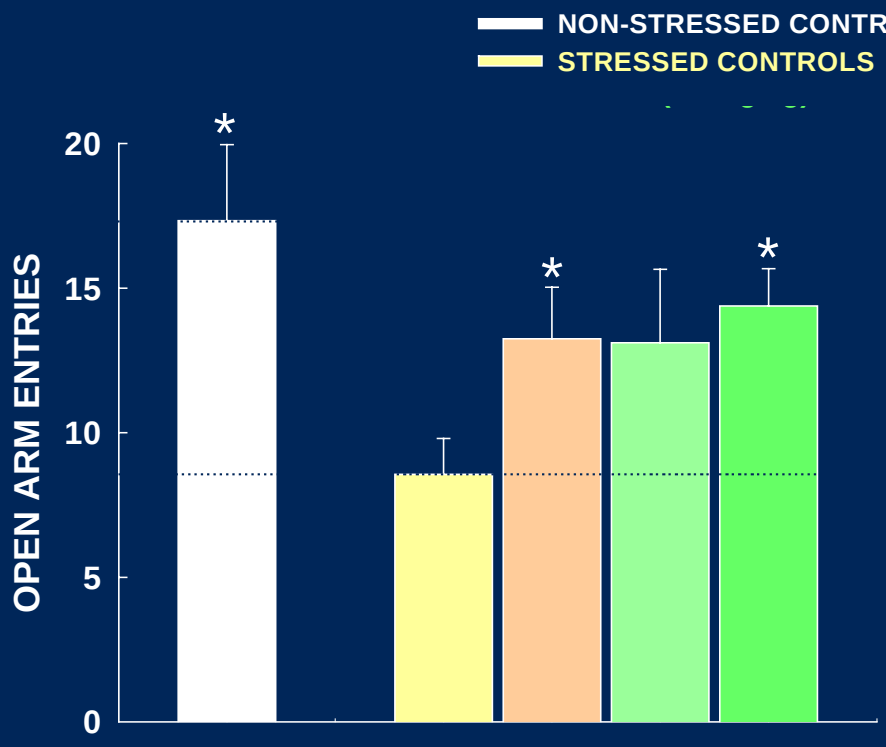


Repeated administration of SSR149415 reversed the degradation of the physical state produced by stress

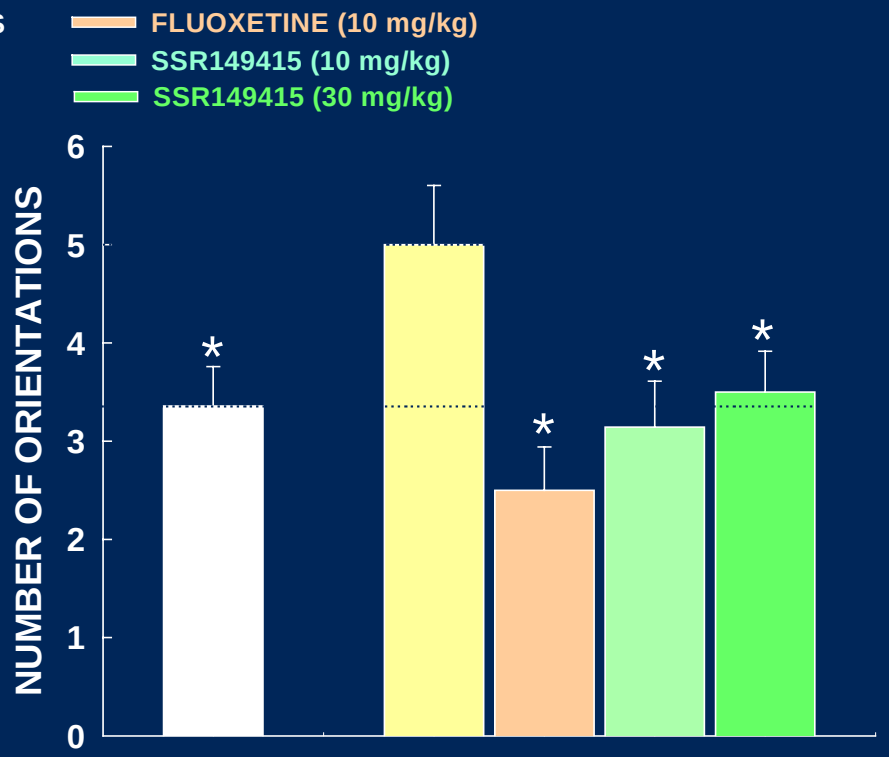
sanofi~synthelabo

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



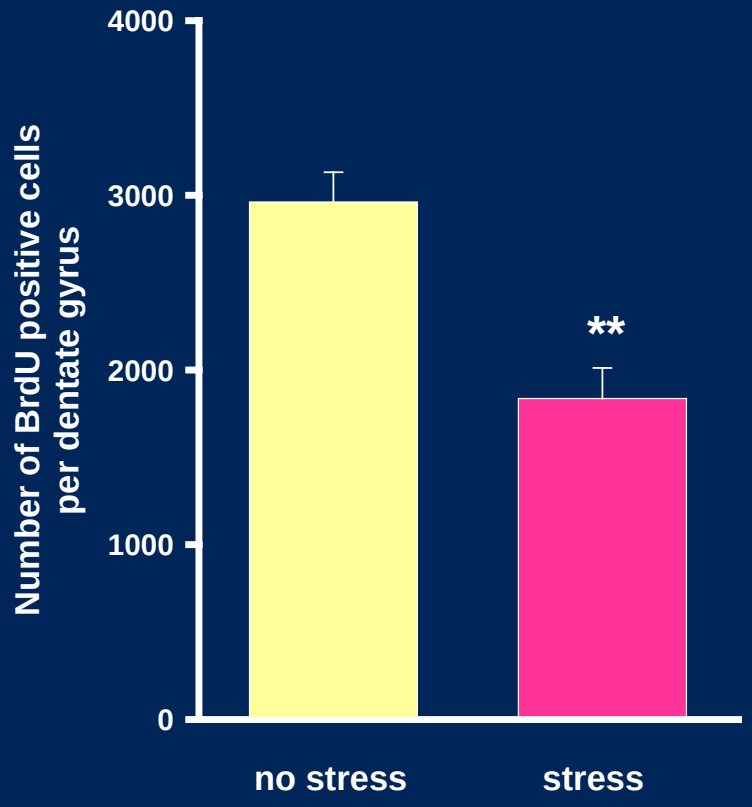
Risk Assessment in the Mouse Defense Test Battery



Repeated administration of SSR149415 reversed anxiety produced by stress

sanofi~synthelabo

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

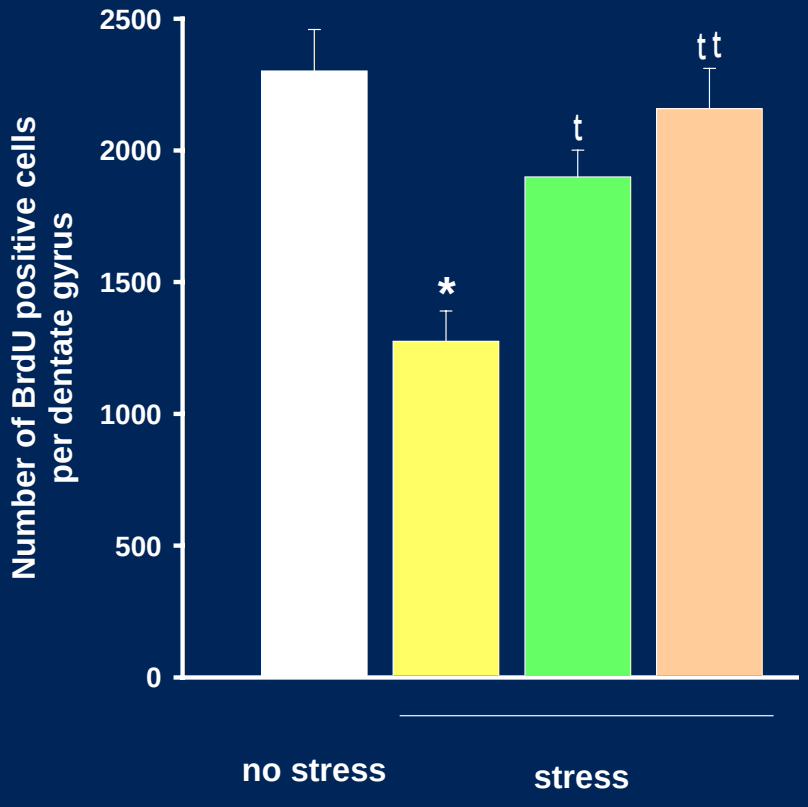


Chronic mild stress decreases the number of BrdU-positive cells

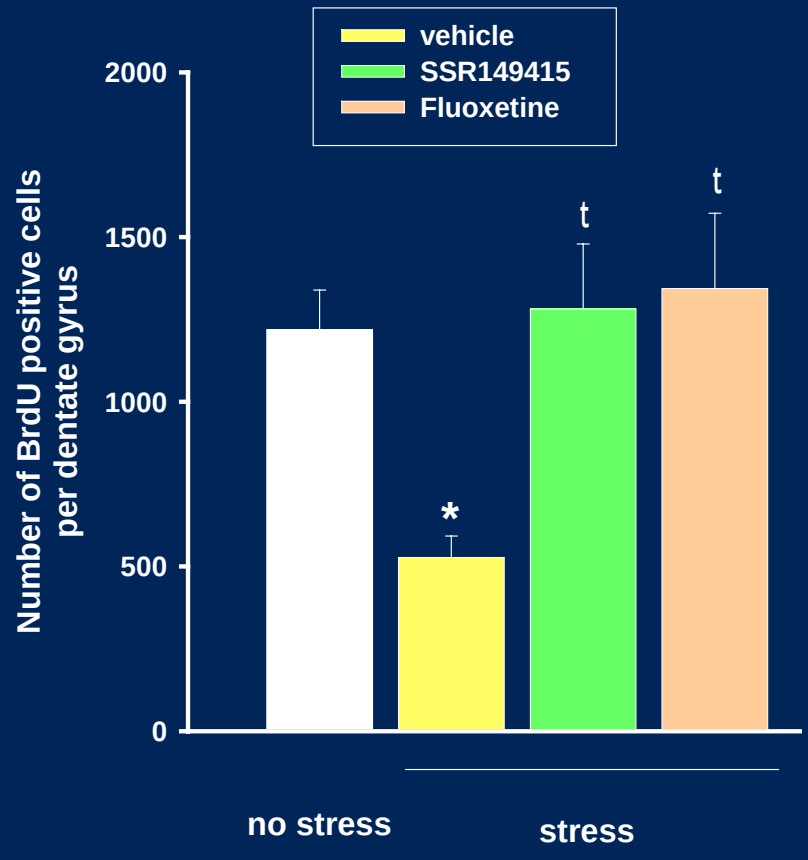
sanofi~synthelabo

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

Cell proliferation (24 h post BrdU)



Neurogenesis (30 days post BrdU)



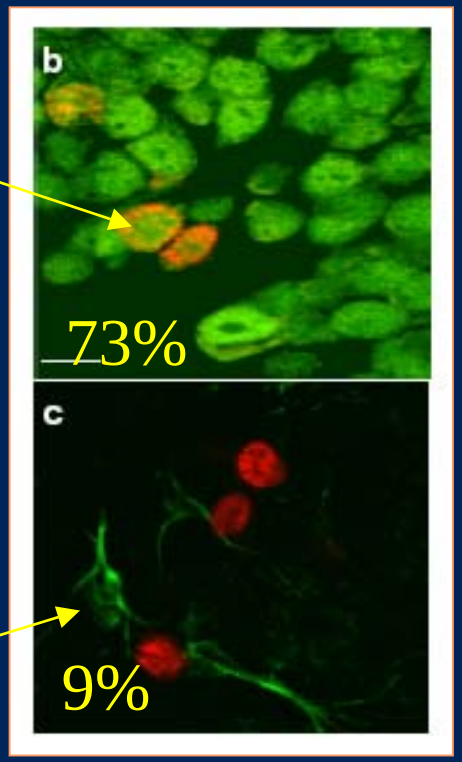
Repeated treatment with SSR149415 prevented stress-induced decrease of cell proliferation in the subgranular zone and neurogenesis in the granular cell layer of the dendate gyrus

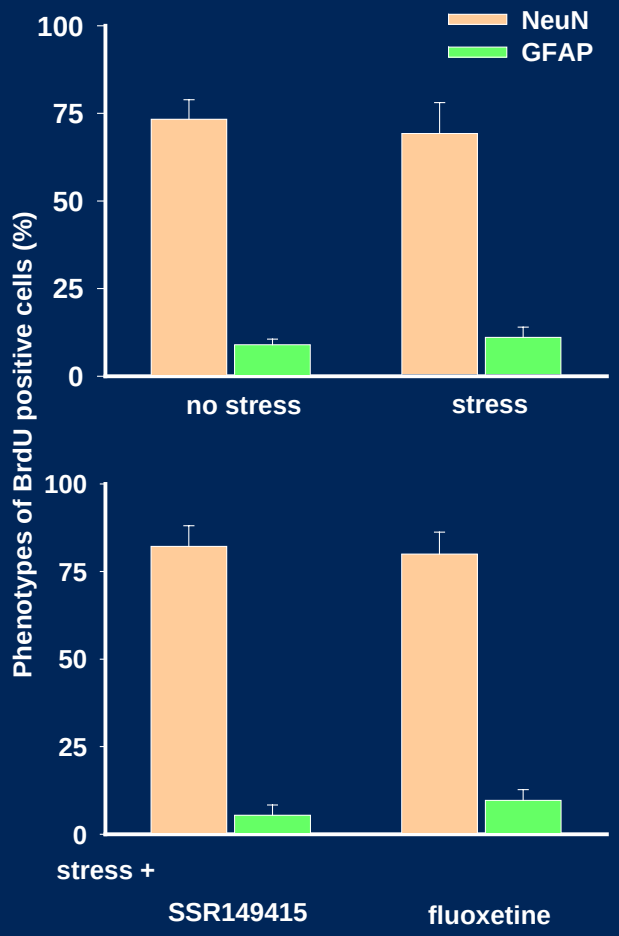
sanofi~synthelabo

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

Mature neuron

Glial cells



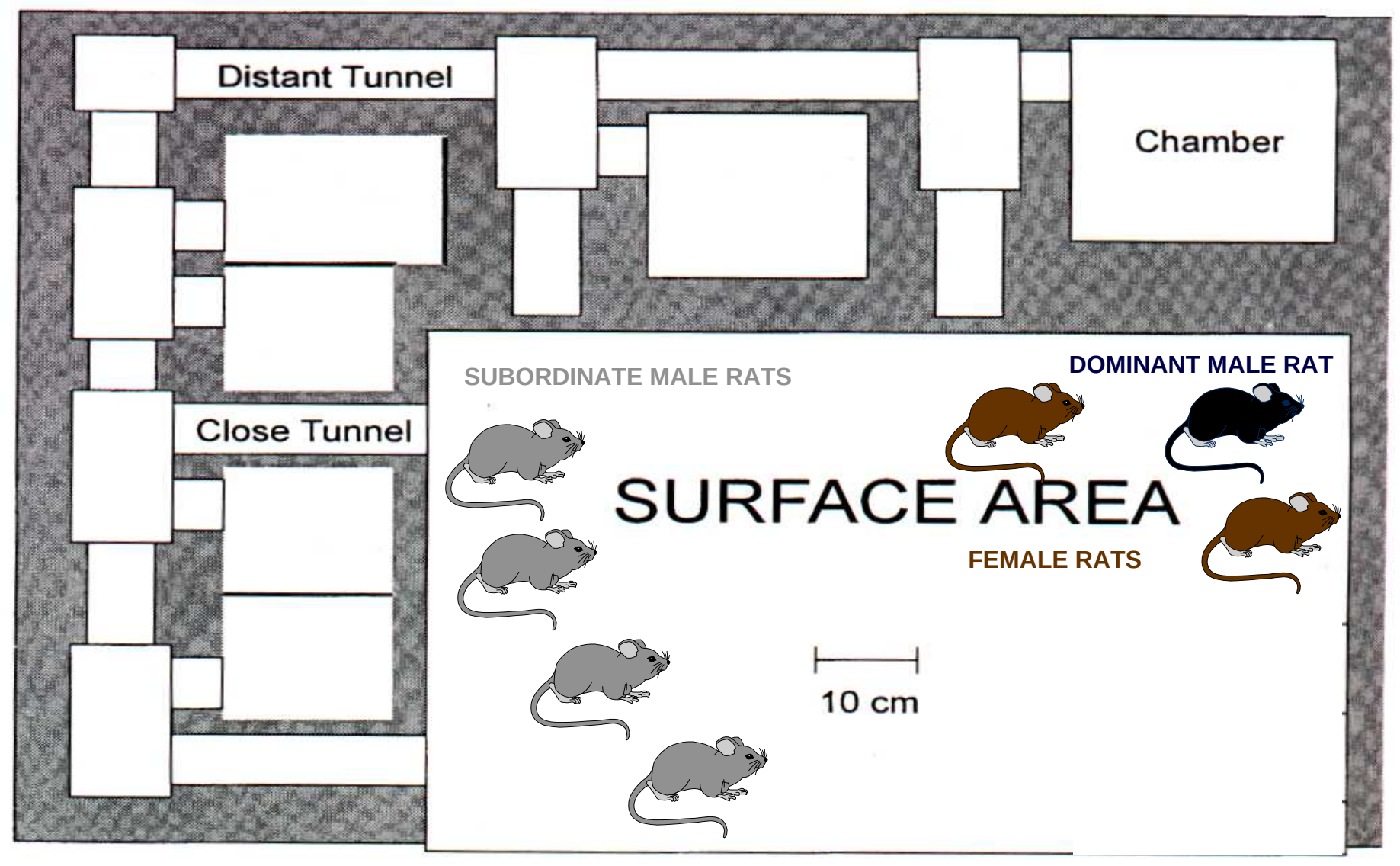


The population of surviving BrdU-positive cells essentially mature into neurons

No difference in phenotypic expression patterns between groups

sanofi~synthelabo

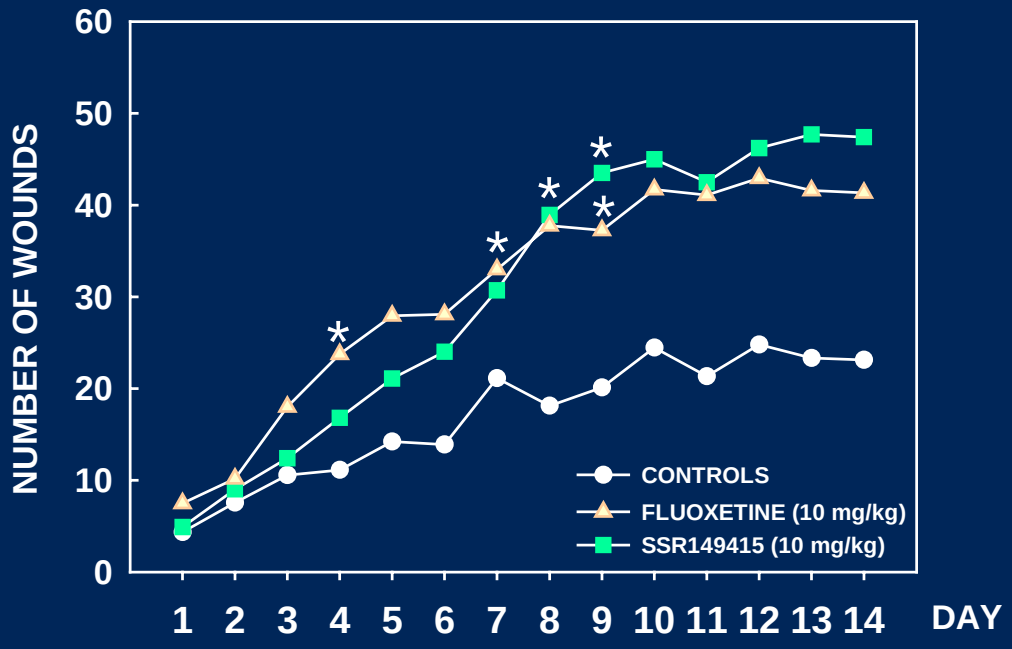
The Visible Burrow System: A Realistic Model of Depression in Rats



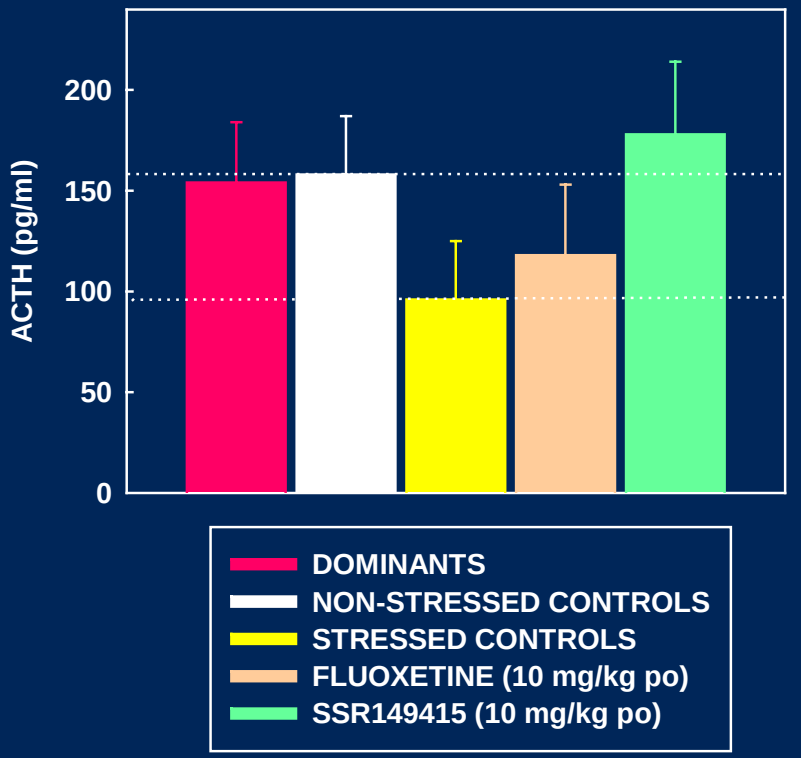
sanofi~synthelabo

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



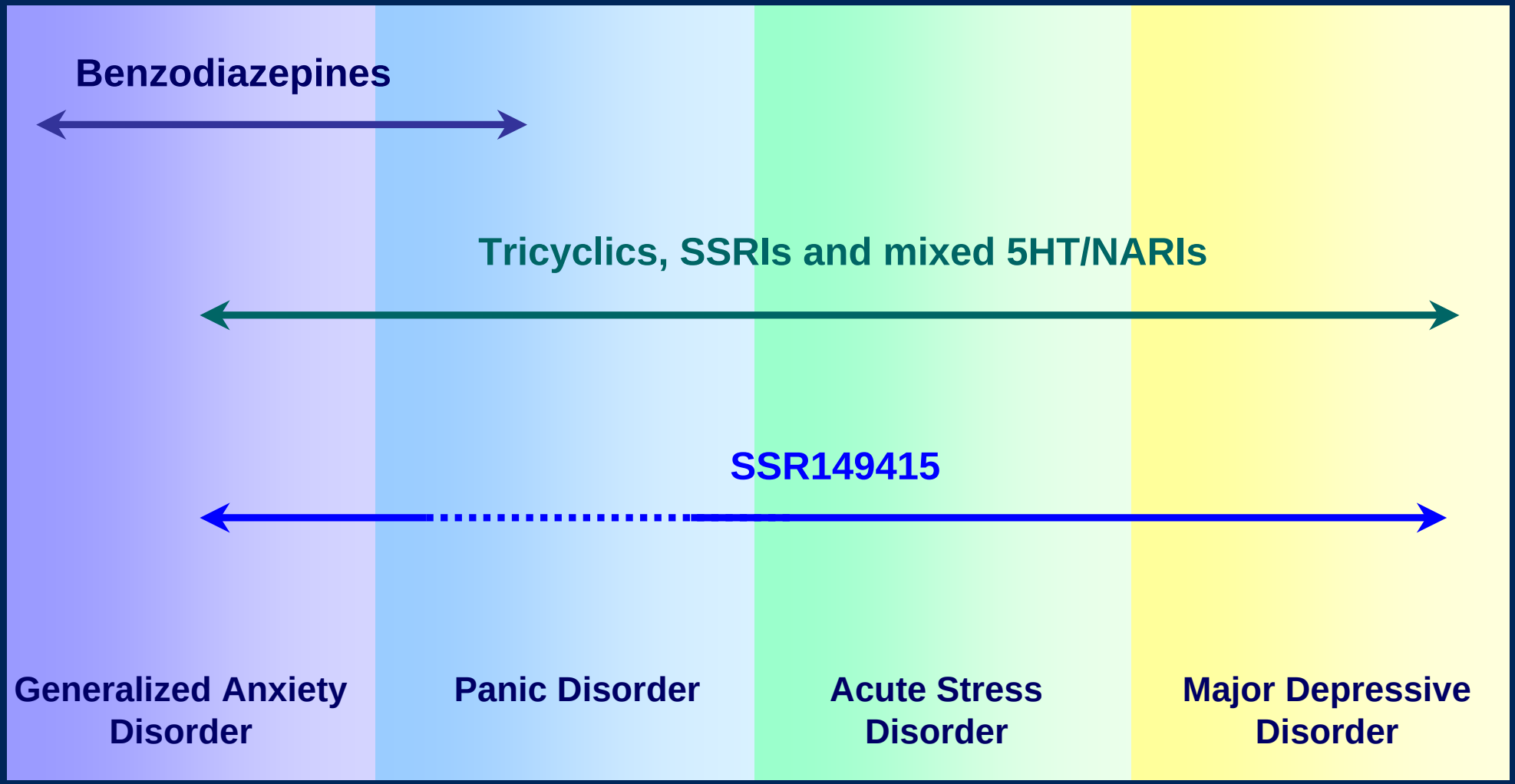
Fluoxetine and SSR149415-treated animals showed higher wound counts than did controls rats

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

Second Joint French – Swiss Meeting on Medicinal Chemistry
Beaune, 1-4 July 2003

sanofi~synthelabo

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

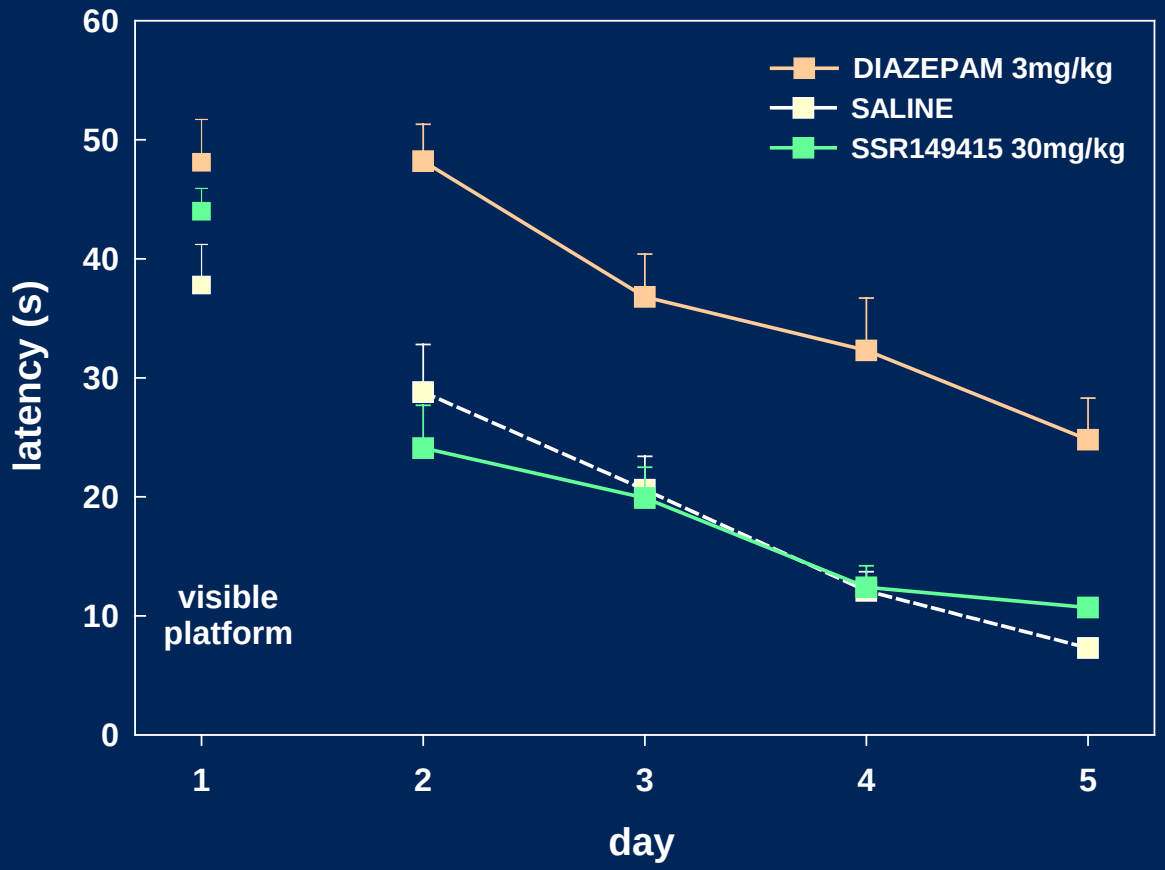


sanofi~synthelabo

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.**

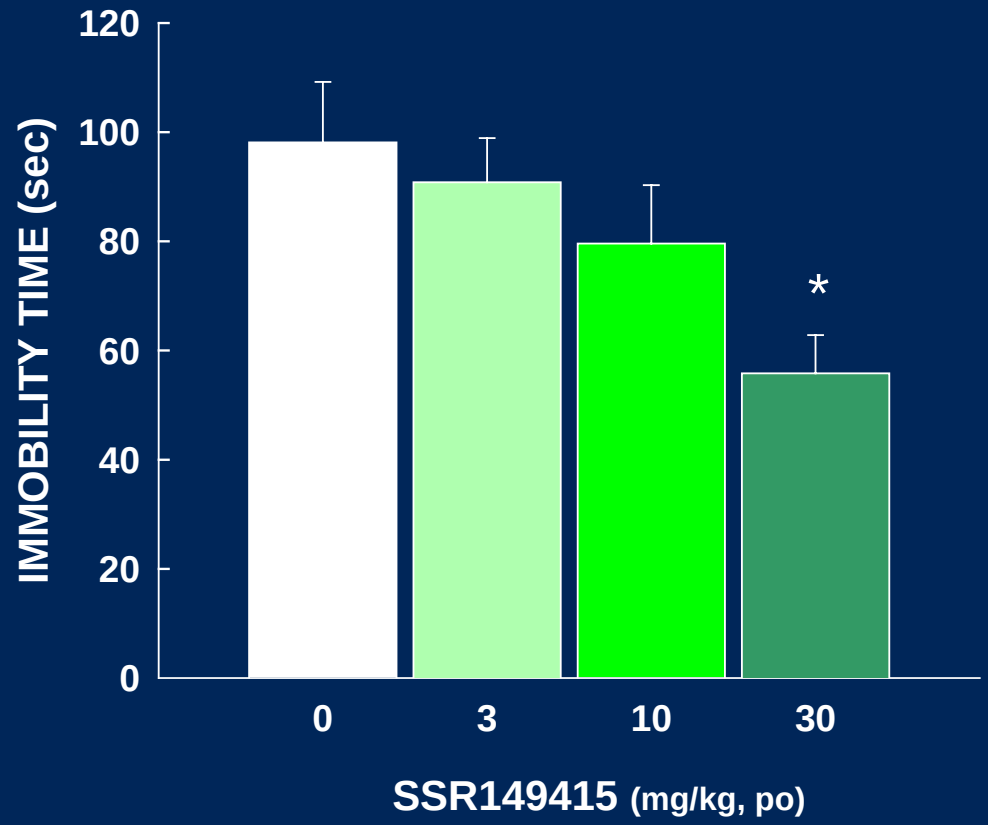
Effects of SSR149415 on spatial memory in mice: The Morris water maze



SSR149415 had no effect on either the acquisition of the test or on recalling the platform position after removal.

sanofi~synthelabo

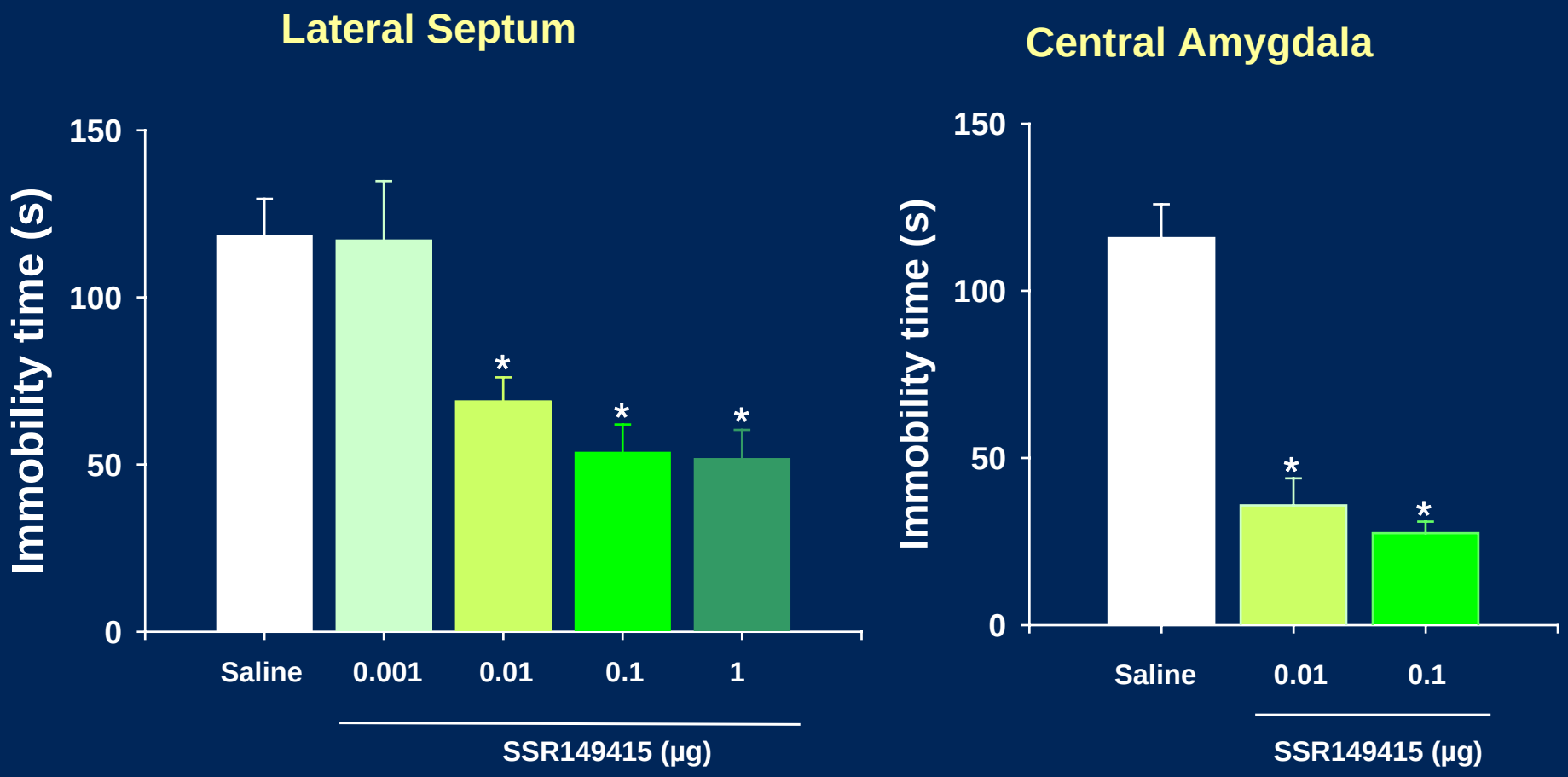
Effects of SSR149415 in the forced-swimming test in hypophysectomized rats



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

sanofi~synthelabo

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

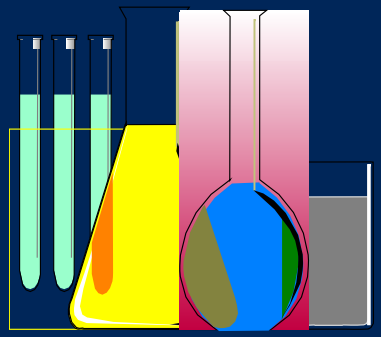
sanofi~synthelabo

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

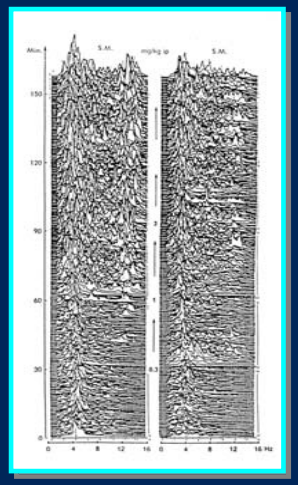


J. WAGNON

BEHAVIORAL STUDIES

M. ARNONE
O. BERGIS
D.C. BLANCHARD
R.J. BLANCHARD
E. DUCONSEILLE
J. SIMIAND
P. SOUBRIE
J. STEMMELIN

ELECTROPHYSIOLOGICAL STUDIES



P. AVENET
M. DECOBERT
D. FRANCON

NEUROCHEMICAL STUDIES

R. ALONSO
L. LUKOVIC
C. SERRADEIL-LE GAL
R. STEINBERG