($F(3,24) = 3.91$, $p < 0.05$) but not for medication order. No significant effects were found in either HAM-H or CGI-I.

Conclusion: Our findings suggests that anti-obsessive medication augmentation with naltrexone associate with exacerbation of OC symptoms in OCD patients. We believe that opiate system is related to OC symptoms and that farther research is needed in order to clarify this connection.

References

[1] Insel TR, Pickar D, 1983. Naloxone Administration in Obssesive-Compulsive disorder: Report of Two Cases. Am J Psychiatry 140:9.
[2] Keuler DJ, Altemus M, Michelson D, Greenberg B, Murphy DL, 1996. Behavioral Effects of Naloxone Infusion in Obsessive-Cumpulsive Disorder. Biol Psychiatry 40: 154–156.
[3] Mangold DL, Peyrot M, Giggey P, Wand GS, 2000. Endogenous opioid activity is associated with obsessive-compulsive symptomology in individuals with a family history of alcoholism. Neuropsychopharmacology 22(6):595–607.

P.4.025 Tiagabine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study

M. Pollack[1]*, M. Van Ameringen[2], H. Snyder[3], C. Brown[3], J. Ondrasik[4], P. Roy-Byrne[5], K. Rickels[6]. [1]*Massachusetts General Hospital, Center for Anxiety & Traumatic Stress Disorders, Boston, USA;* [2]*McMaster University Medical Centre, Dept. of Psychiatry & Behavioural Neurosciences, Canada;* [3]*Cephalon Inc., Clinical Research, USA;* [4]*Cephalon Inc., Biometrics, USA;* [5]*University of Washington School of Medicine, Psychiatry and Behavioural Sciences, USA;* [6]*University of Pennsylvania, Human Behavior & Psychiatry, USA*

Introduction: Gamma-aminobutyric acid (GABA) plays a role in the pathophysiology and treatment of generalized anxiety disorder (GAD). Tiagabine, a selective GABA reuptake inhibitor (SGRI), increases synaptic GABA availability via GAT-1 GABA transporter inhibition. The efficacy and tolerability of tiagabine was evaluated in adults with generalized anxiety disorder (GAD).

Method: This 8-week, randomized, double-blind, placebo-controlled study enrolled adults meeting DSM-IV criteria for GAD. Tiagabine was administered in divided doses, one dose with breakfast and one dose in the evening (approximately 9 PM) with a snack. Tiagabine was initiated at 4 mg/day for the first week and then individually titrated through week 6, in weekly increments of up to 4 mg to a maximum dose of 16 mg/day. The dose established at week 6 could not be increased during weeks 7 and 8. Efficacy assessments included the Hamilton Rating Scale for Anxiety (HAM-A), Clinical Global Impression (CGI) scale, and Sheehan Disability Scale (SDS). Adverse events, sexual functioning, and change in weight and depressive symptoms were monitored.

Results: A total of 266 patients (tiagabine, n = 134; placebo, n = 132) received at least one dose of study drug and were included in the safety analysis. Of these, 260 patients (tiagabine, n = 130; placebo, n = 130) had at least one post-baseline assessment and were included in the efficacy analysis. Tiagabine reduced symptoms of GAD, with an early onset of effect. Observed case analysis showed significant mean reductions from baseline in HAM-A total score compared with placebo at weeks 1 (−5.3 vs −3.1, respectively; $P < 0.001$) and 8 (−13.2 vs −10.7; $P < 0.05$). Tiagabine reduced mean HAM-A total score across entire study period ($P < 0.01$ versus placebo; mixed models repeated measures analysis). Tiagabine was generally well tolerated and was not associated with changes in weight, sexual functioning, or depressive status. Symptoms of a discontinuation syndrome following gradual taper were not observed.

Conclusion: These results suggest that tiagabine may be a useful treatment option for adult patients with GAD.

P.4.026 The anticonflict and antidepressant-like effects of proproten are serotonin dependent

J.L. Dugina[1]*, T.A. Voronina[2], A.V. Martyushev-Poklad[3], S.A. Sergeeva[3], I.A. Heifets[3], O.I. Epstein[3]. [1]*Scientific Department, Moscow, Russian Federation;* [2]*Research Institute of Pharmacology RAMS, Lab of Pscycopharmacology, Russian Federation;* [3]*"Materia Medica Holding" Research and Production Company, Scientific Department, Russian Federation*

It is not surprising that a diversity of mechanisms is involved in the induction and inhibition of anxious and depressive states. Not only monoamines, GABA and glutamate, but also many other modulators including serotonin, dopamine etc have been implicated in these disorders. Proproten (ultra-low doses of antibodies to S-100 protein), first marketed in Russia as antialcoholic drug, has displayed its anxyoliyic properties in several paradigms: Vogel conflict test, open-field test, elevated plus maze. GABA-ergic system was proved to be involved in the realization of anxiolytic activity of proproten (Voronina et al., 2003).

The aim of the presented research was to study the possible involvement of serotonergic system in anticonflict (Vogel test) and antidepressant-like (forced swim test) activities of proproten. All experiments were carried out on white male outbred rats (220–250 g). Proproten (2.5 ml/kg, i.p.), diazepam (2 mg/kg, i.p.) or amitriptyline (15 mg/kg, i.p.) were given 30 min before the experiments. Ketanserin (1 mg/kg), serotonin 5-HT_2 receptor antagonist, and 5-hydroxy-l-tryptophan (5-HTP, 50 mg/kg), a precursor to serotonin, were injected i.p. 10 min before the administration of proproten. In Vogel conflict assay, both proproten and diazepam increased punished response rates (shown in Table). The effect of proproten was partially reversed by ketanserin or 5-HTP. In forced swim test, the antidepressant-like effect of proproten, exceeding that of amitriptyline, was completely inverted by 5-HTP and was significantly reduced by ketanserin (shown in Table).

Groups	Number of punished responses (Vogel test)	Number of wheel rotations (Forced swim test)
Vehicle, 2.5 ml/kg	102.2±15.06	73.0±25.19
Proproten, 2.5 ml/kg	372.6±45.18*	159.5±29.77*
Diazepam, 1 mg/kg	372.6±45.18*	ND
Amitriptyline, 15 mg/kg	ND	119.13±19.16*
5-HTP, 50 mg/kg	135.0±33.15	117.1±24.87*
Ketanserin, 1 mg/kg	224.5±31.7*	146.6±30.16*
Proproten, 2.5 ml/kg + 5-HTP, 50 mg/kg	259.2±48.4	80.5±18.14#
Proproten, 2.5 ml/kg + ketanserin, 1 mg/kg	168.7±40.12#	102.9±44.36

*$p < 0.05$ vs vehicle; #$p < 0.05$ vs proproten alone.

To conclude, although the underlying mechanisms are still unclear, proproten can be regarded as a modulator of serotonergic system. Proproten as well as other drugs affecting serotonin

and GABA turnover are of potential application in treating the depression and anxiety.

References

[1] Voronina T.A, Epshtein O.I., Molodavkin G.M., Sergeeva S.A., Kraineva V.A., 2003. Spectrum of psychotropic effects and mechanism of action of ultra low doses of the antibodies to S-100 protein (proproten). Radiats. Biol. Radioecol. 43(3), 291–293.

P.4.027 NK1 receptor occupancy and anxiolytic-like effect of the novel NK1 receptor antagonist Vestipitant (GW597599) in gerbil

R. Carletti*, C. Griffante, C. Pozzato, A. Zanoncelli, S. Melotto, P.A. Gerrard, D.G. Trist, E. Ratti, M. Corsi. *GlaxoSmithKline, Psychiatry CEDD, Verona, Italy*

Objectives: Preclinical and clinical evidence suggests that NK1 receptors are involved in neuronal circuits related to stress and mood disorders. In the present study the anxiolytic-like effects of selective NK1 receptor antagonists, including GR205171, Aprepitant (MK869) and Vestipitant (GW597599), have been investigated in the social interaction test (SI) in the gerbil. The relationship between the induced anxiolytic effect and the central NK1 receptor occupancy (RO) was defined.

Methods: Pairs of male Mongolian gerbils (60–80 g) were placed in the test arena and their active SI and spontaneous locomotor activity (LMA) were recorded for five minutes [1]. A significant increase of the time spent in SI suggested an induced anxiolytic-like effect, in the absence of sedative effect as measured by LMA. Diazepam was utilised as a standard anxiolytic drug. Immediately after the test, gerbils pre-treated with NK1 receptor antagonists or vehicle were sacrificed and the brains were quickly removed, frozen and processed for *ex vivo* autoradiography to determine the NK1 RO. Total binding (0.3 nM [3H]-GR205171) was determined in coronal brain sections (12μm) at a restricted incubation of 10 min to minimise dissociation and sections were then exposed to Fuji imaging plates for 10 days. *Ex vivo* binding was measured in striatum.

Results: Diazepam (1 mg/kg p.o.) induced a significant anxiolytic-like effect (+59% increase in SI vs control, $p < 0.01$). GR205171 induced a significant anxiolytic-like effect at 0.3 mg/kg (+54.1%, vs control, $p < 0.01$) with a level of NK1 RO in the striatum of 98.0%. The non-effective doses of GR205171 (0.01 and 0.03 mg/kg) in the SI test produced levels of NK1 RO of 42.7% and 86.0%, respectively. Aprepitant induced a significant increase in SI at 3 mg/kg (+50.5%, vs control, $p < 0.01$) with a level of NK1 RO of 96.6%. The non-effective doses of Aprepitant (0.3 and 1 mg/kg) in the SI test produced levels of NK1 RO in the striatum of 37.1% and 68.5%, respectively. Vestipitant induced a significant increase in SI at 1 and 3 mg/kg (+91.3% and +112.4%, $p < 0.01$, vs control, respectively) and the corresponding NK1 RO were 96.2% and 97.8%. The non-effective doses of Vestipitant (0.1 and 0.3 mg/kg) in the SI test produced levels of NK1 RO in the striatum of 54.6% and 85.5%, respectively.

Conclusions: The present results confirm the anxiolytic-like profile induced by various NK1 receptor antagonists in preclinical species. Moreover, the three selective and potent NK1 receptor antagonists tested suggest that full (>95%) NK1 RO is necessary to elicit a significant effect in the gerbil SI, which support the relevance of preclinical plasma exposure/RO measurements to define dose ranges for clinical studies [2].

References

[1] Cheeta S. et al., 2001, Brain Research 915: 170–75.
[2] Hargreaves R. et al., 2002, J. Clin. Psychiatry 63 (11): 18–24.

P.4.028 Behavioral evidence that chronic treatment with alprazolam sensitizes serotonin-2a receptors in the rat dorsal periaqueductal gray matter

H. Zangrossi Jr.[1]*, V.C. Bortoli[1], R.L. Nogueira[2]. [1]*School of Medicine of Ribeirão Preto, University of São Paulo, Pharmacology, Ribeirão Preto, Brazil;* [2]*University Estácio de Sá, Comparative Psychology, Brazil*

Purpose of the study: The dorsal periaqueductal gray matter (DPAG) has been implicated in the mediation of escape, a defensive behavior that has been related to panic disorder. Intra-DPAG injection of serotonin or drugs that mimic its effects inhibits escape induced by electrical/chemical stimulation of this brainstem area [1]. Long-term treatment with the classical antipanic agent imipramine enhances the inhibitory effect of intra-DPAG administration of the 5-HT_{1A} and 5-HT_{2A} receptor agonists, respectively, 8-OH-DPAT and DOI on escape evoked by DPAG stimulation [2]. Therefore, chronic imipramine treatment sensitizes both 5-HT_{1A} and 5-HT_{2A} receptors in the DPAG, implicating these changes in the mode of action of antipanic drugs. In the present study we investigated whether sensitization of 5-HT_{1A} and 5-HT_{2A} receptors in the DPAG is also observed after chronic administration of alprazolam, a benzodiazepine receptor agonist clinically effective in treating panic disorder. It has been shown that alprazolam affects 5-HT neurotransmition in other anxiety-related areas such as the hippocampus [3].

Methods: Male Wistar rats, subchronically (3–6 days, n = 12–15) or chronically (14–17 days, n = 10–14) treated with alprazolam (2 mg/kg, i.p.) or vehicle solution were intra-DPAG injected (0.2 μL) with 8-OH-DPAT (8 nmoles), DOI (16 nmoles), the benzodiazepine receptor agonist midazolam (MDZ; 20 nmoles) or saline. The threshold of aversive electrical stimulation that applied to the DPAG evokes escape behavior was measured before and after the microinjection of these agonists.

Results: Intra-DPAG injection of 8-OH-DPAT, DOI and midazolam raised the threshold of aversive electrical stimulation for inducing escape in all groups of animals tested. However, the effect of DOI, but not of midazolam was significantly higher ($p < 0.05$) in animals receiving long-term treatment with alprazolam [aversive threshold (mean ± SEM, μA): veic/sal = 5.5±1.6; veic/DOI = 29.0±2.4; veic/MDZ = 34.8±2.9; alpra/sal = 6.0±1.1; alpra/DOI = 54.0±5.3; alpra/MDZ = 40.0±7.0]. Chronic treatment with alprazolam tended ($p = 0.09$) to increase the inhibitory effect of 8-OH-DPAT on escape [veic/8-OH = 30.0±4.0; alpra/8-OH = 42.4±5.4]. These changes were not observed in animals subchronically treated with alprazolam.

Conclusions: As reported previously with the tricyclic antidepressant imipramine [2], long-term treatment with alprazolam sensitizes 5-HT_{2A} receptors in the DPAG, strengthening the view that these receptors are involved in the mode of action of antipanic drugs.

Support: Fapesp, CNPq, Brazil.

References

[1] Graeff, F., 2002. On serotonin and experimental anxiety. Psychopharmacology 163, 467–476.