P.0274
NEUROSCIENCE APPLIED 1 (2022) 100112 100356
Ulotaront improves metabolic parameters in rodent models of weight gain and hyperglycemia

C. Zeni [1], N. Dedic [2], P. Jones [2], S. Wu [3], C. Anacker [3], E. Hajos-Korcsok [2], C. Synan [4], S. Milanovic [5], S. Hopkins [5], L. Bristow [2], K. Koblan [6]. [1] *Sunovion Pharmaceuticals Inc., Medical Affairs, Fair Haven, United States;* [2] *Sunovion Pharmaceuticals Inc., Pharmacology, Marlborough- MA, United States;* [3] *Columbia University Irving Medical Center CUIMC, Department of Psychiatry, New York- NY, United States;* [4] *Sunovion Pharmaceuticals Inc., Toxicology, Marlborough- MA, United States;* [5] *Sunovion Pharmaceuticals Inc., Translational Medicine, Marlborough- MA, United States;* [6] *Sunovion Pharmaceuticals Inc., Chief Scientific Officer, Marlborough- MA, United States*

Background: Ulotaront (SEP-363856) is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A agonist activity currently in Phase 3 clinical trials for the treatment of schizophrenia. Metabolic Syndrome, characterized by central obesity, dyslipidemia, hypertension, and hyperglycemia, is highly prevalent in patients with schizophrenia and can be induced or exacerbated by antipsychotic drugs (APDs). The need for novel treatments that lack APD class-specific metabolic side effects is therefore apparent. As a new pharmacological class, ulotaront has no significant activity at receptors commonly associated with APD-induced metabolic alterations (i.e. D2, 5-HT2C, H1 and M3). Recent preclinical evidence has identified TAAR1 as novel regulator of metabolic control and a promising target for treating obesity and type 2 diabetes. Here we evaluated the risk-benefit profile of ulotaront for the treatment of schizophrenia by assessing its effects on metabolic parameters in rodent models of iatrogenic weight gain and hyperglycemia.

Methods: Effects of 15-day oral ulotaront treatment on body weight (BW), food intake and metabolic parameters were investigated in rats on a high-fat diet (HFD). In addition, body weight effects were determined in a rat (8-day treatment) and mouse (21-day treatment) model of olanzapine-, and corticosterone-induced BW gain, respectively. Glucose tolerance was assessed in C57Bl6 and diabetic db/db mice following acute oral dosing. The acetaminophen absorption test was used to evaluate effects on gastric emptying in C57Bl6 mice. To obtain insights into the neurocircuits modulated by ulotaront, whole-brain 3D c-fos imaging was performed in C57Bl6 mice.

Results: Administration of ulotaront to rats on a HFD resulted in a dose-dependent reduction in BW, food intake and liver triglyceride content compared to vehicle controls. A more rapid reversal of olanzapine-induced BW gain and food intake was observed in rats switched to ulotaront treatment compared to vehicle alone. Consistent with the BW-lowering effects in rats, chronic treatment with ulotaront normalized corticosterone-induced BW gain in mice. Acute ulotaront dosing dose-dependently reduced plasma glucose excursion in C57Bl6 and diabetic db/db mice during an oral glucose tolerance test (oGTT). Neither glucose nor insulin levels were changed in response to ulotaront during an ivGTT. Acute TAAR1 activation delayed gastric emptying in mice, which is likely the main mechanism driving reductions in glucose excursion during the oGTT. Ulotaront increased neuronal activity (c-fos expression) in several brain regions associated with the regulation of food intake and integration of peripheral metabolic signals, which was distinct from the signature produced by the APD haloperidol.

Conclusion: Our data indicate that ulotaront not only lacks APD-induced metabolic liabilities but can reduce BW and improve glucose tolerance in rodent models. The underlying mechanisms are not fully elucidated but may include TAAR1-mediated peripheral effects on glucose homeostasis and gastric emptying, and/or direct modulation of homeostatic and hedonic neurocircuits regulating energy balance. The beneficial metabolic effects of ulotaront suggest a substantially improved risk-benefit profile compared to established APDs. Thus, TAAR1 agonists may not only represent a novel therapeutic class for the treatment of schizophrenia, but potentially also for metabolic disorders.

Conflict of interest

Disclosure statement:

P.0275
NEUROSCIENCE APPLIED 1 (2022) 100112 100357
Pharmacological inhibition of nitric oxide synthase 1 adaptor protein in adult offspring after maternal immune activation

D. Esen-Sehir [1,2], A.Y. Yotova [1,2], L.L. Li [3], A. Reif [1], M.J. Courtney [3], F. Freudenberg [1]. [1] *Laboratory of Translational Psychiatry, Department of Psychiatry-Psychosomatic Medicine and Psychotherapy- Goethe University Frankfurt- University Hospital, Frankfurt am Main, Germany;* [2] *Faculty of Biological Sciences, Goethe University Frankfurt, Frankfurt am Main, Germany;* [3] *Neuronal Signalling Laboratory-Turku Centre for Biotechnology, University of Turku, Turku, Finland*

Background: Glutamatergic neurotransmission has long been associated with the pathophysiology of psychiatric disorders, including schizophrenia, and might be exploited for pharmaceutical interventions. One of the possible targets is nitric oxide synthase 1 adaptor protein (NOS1AP), which is found to be upregulated in patients with schizophrenia [1]. Moreover, NOS1AP interacts with further downstream effectors of NMDA receptor signalling, like p38 MAPK, RasD1, or Scribble [2, 3] that have also been associated with complex neuropsychiatric pathologies. Thus, we have identified small molecules targeting NOS1AP interactions, and a previous in vitro investigation showed a rescue of morphological deficits caused by NOS1AP overexpression [4]. Here, we investigate the effects of this small molecule, naringenin, in an environmental mouse model for schizophrenia utilising maternal immune activation (MIA).

Methods: MIA was induced on the ninth gestational day by administering 5 mg/kg, IV of the viral mimetic polyinosinic:polycytidylic acid [poly(I:C)] or PBS in C57Bl/6J wild-type dams, mimicking pathogen-induced infection during pregnancy [5]. For chronic intracerebroventricular delivery of the small molecule naringenin or vehicle only, we implanted 12-week-old offspring (N=5-11/group/sex) with osmotic minipumps, delivering 30 mM naringenin at a constant rate of 0.15 µl/hr into one of the lateral ventricles. One week after surgery, mice were subjected to a comprehensive behavioural battery to examine schizophrenia-linked behaviours. Data were statistically analysed by three-way ANOVA with sex, MIA and treatment as fixed factors.

Results: Multiple interaction effects reminiscent of schizophrenia-like symptoms were found altered between groups. Prenatally immune challenged male mice showed a significant decrease in exploratory behaviour (i.e. time in the open arm) vs untreated controls (p=0.03) and increased anxiety-related behaviour (i.e. time in the light compartment; p=0.046). The treatment with naringenin showed a trend towards normalization of this behaviour (p=0.06), equally present in female PBS-offspring treated with naringenin (p=0.077). Vertical activity in the open field was decreased in naringenin-treated mice (p=0.026), whereas horizontal activity remained unaltered (p=0.795). An interaction effect of sex and treatment was observed in spatial novelty preference (p=0.002), with female naringenin-treated mice showing less preference while male naringenin-treated mice showed an increased preference compared to their vehicle-treated controls. Depression-like behaviours were assessed by analysing sucrose preference and nest-building behaviour. Sex and treatment exerted a significant interaction effect (p=0.034), with male naringenin-treated mice showing increased anhedonia compared to vehicle-treated. However, treatment with naringenin resulted in decreased nest-building scores (p=0.048). Sensorimotor gating measured by prepulse inhibition test remained unaffected by MIA or treatment (p>0.177).

Conclusions: Unexpectedly, there was no interaction effect between MIA and treatment, suggesting no beneficial effect of naringenin in this model. However, naringenin affects different symptom domains related to schizophrenia. While this molecule requires further in vivo validation, our results indicate that NOS1AP may present a promising tangible target for additional treatment options. Analyses of naringenin effects in a NOS1AP-overexpression mouse model are ongoing and might offer further insights into application options of naringenin.

References

[1] Brzustowicz, L. M. (2008). NOS1AP in schizophrenia. Current Psychiatry Reports, 10(2), 158–163. https://doi.org/10.1007/s11920-008-0027-0 [2] Courtney, M. J., Li, L. L., & Lai, Y. Y. (2014). Mechanisms of NOS1AP action on NMDA receptor-nNOS signaling. Frontiers in Cellular Neuroscience. https://doi.org/10.3389/fncel.2014.00252 [3] Wang, J., Jin, L., Zhu, Y., Zhou, X., Yu, R., & Gao, S. (2016). Research progress in NOS1AP in neurological and psychiatric diseases. Brain Research Bulletin. Elsevier Inc. https://doi.org/10.1016/

j.brainresbull.2016.05.014 [4] Esen-Sehir, D., Sauerland, C., Li, L., Courtney, M. J., Reif, A., & Freudenberg, F. (2021). P.103 Targeting nitric oxide synthase 1 adaptor protein rescues schizophrenia-related alterations in dendritic morphology. European Neuropsychopharmacology, 44, S2–S3. https://doi.org/ 10.1016/j.euroneuro.2021.01.010 [5] Yotova, A.Y., Li, L., Slattery, D.A., Reif, A., Courtney, M.J. and Freudenberg, F.(2020). P. 076 Synaptic proteome changes in the hippocampus of prenatally immune-challenged adult mice correspond to behavioural impairments reminiscent of neuropsychiatric developmental disorders. European Neuropsychopharmacology, 40, pp.S49-S50.

Conflict of interest

Disclosure statement:

P.0276

The effect of quinpirole on locomotor activity in home cage monitoring system

J. Park [1], K. Kim [1], H. Suh [1], H. Lim [1], E. Moon [1,2]. [1] *Pusan National University Hospital, Psychiatry and Biomedical Research Institute, Busan, Korea- Rep;* [2] *Pusan National University School of Medicine, Psychiatry, Yangsan, Korea- Rep*

Introduction: The dopaminergic system has substantial influences on our body, such as on motor control, cognitive function, reward and motivation. Among those that are affected by dopamine, the relationship between dopamine and locomotor activity is being considered importantly and from the 1980s, the connection between locomotor activity and dopamine has been studied. As dopamine is closely linked to locomotor activities, studies on locomotor activities using dopaminergic agents that work on dopamine receptors are widely done as well. Quinpirole is a D2, D3 receptor agonist that is known to increase locomotor activities, however there is a lack of study on a mice model that there was a necessity to investigate the relationship between quinpirole and locomotor activities in a mice model.

Aim: We aimed to examine the effects of single administered quinpirole on locomotor activities in mice.

Methods: The locomotor activities of ten male Institute Cancer Research (ICR) mice were measured by infrared motion detectors in home cages. Infra-red detectors, Mlog system (Biobserve GmbH, Bonn, Germany) are devices that allows to observe the locomotor activities of the mice continuously in their home cages for 24 hours a day for a week. The dark-light phases were managed with 12-hour intervals by a lighting system (Philips, Burlington, MA, U.S.) which is controlled by a computer software. The lights were turned on at 5:00 a.m. to maintain a light phase for 12-hours, and turned off at 5:00 p.m. to maintain a dark phase for 12-hours. Quinpirole was injected at concentration of 0.5mg/kg intraperitoneally at 5:00 p.m. when a light phase is over. The locomotor activities data was summed for every 12 hours and 24 hours and compared the changes in activities before and after the administration of quinpirole. Also. to represent the entrainment of circadian rest-activity rhythm, the difference and ratio of locomotor activities in dark and light phases were calculated. Statistical validity was confirmed by the Wilcoxon Signed Rank Test using R Statistical software (version 4.1.3, 2021).

Summary of Results: After the quinpirole administration, the locomotor activities were increased in dark phase (V=7, p=0.037) and decreased in light phase (V=50, p=0.019) compared to the baseline locomotor activities which was measured before the injection. However, there was no significant change in total locomotor activities (V=12, p=0.131) after quinpirole was administered. On the other hand, dark-light phases difference (V=4, p=0.014) and ratio (V=3, p=0.010) increased significantly after the injection.

Conclusion: This study suggests that administration of quinpirole might increase the locomotor activities in dark phase but decrease in light phase without increasing the total locomotor activities. As the difference and ratio of dark-light phases increased after the quinpirole injection, it indicates quinpirole injection entrains the circadian rest-activity rhythm of locomotor activities. Therefore, quinpirole can be a drug that mediates locomotor activity as a dopamine agonist as well as a modulator of the circadian rhythms.

No conflict of interest

P.0277

Nigella sativa seeds oil alleviates lipopolysaccharide-induced memory impairment

M. Vlasheva [1], A. Mihaylova [2], N. Doncheva [2], M. Katsarova [1], S. Dimitrova [3], I. Kostadinov [4]. [1] *Faculty of Pharmacy- Medical University of Plovdiv, Department of Bioorganic Chemistry, Plovdiv, Bulgaria;* [2] *Faculty of Pharmacy- Medical University of Plovdiv, Department of Pharmacology- Toxicology and Pharmacotherapy, Plovdiv, Bulgaria;* [3] *Faculty of Pharmacy- Medical University of Plovdiv- Research Institute- Medical University of Plovdiv, Department of Bioorganic Chemistry, Plovdiv, Bulgaria;* [4] *Faculty of Medicine- Medical University of Plovdiv, Department of Pharmacology and Clinical Pharmacology, Plovdiv, Bulgaria*

Background: the therapeutic properties of Nigella sativa (NS), commonly known as black seeds or black cumin, have been used for millennia. Experimental and clinical findings have demonstrated that NS and its active constituent thymoquinone have neuroprotective properties. Improvement of attention, memory and cognition was observed in healthy male volunteers [1]. Hydro-alcoholic extract from the seeds prevents scopolamine-induced spatial memory impairment in experimental animals [2]. Thymoquinone (TQ) decreases oxidative stress in the hippocampus, stimulates neurogenesis and improves memory in rats [3]. It was shown that NS seed extract has protective effect against lipopolysaccharide (LPS)-induced memory and synaptic plasticity impairment in the rat hippocampus [4]. Systemic administration of LPS leads to neuroinflammation and cognitive impairment used as an experimental model of neurodegenerative disorders [5]. The aim of the current study was to investigate the memory improving properties of NS seeds oil in rats with LPS-induced neuroinflammation.

Methods: 40 male Wistar rats were randomly divided into 5 groups (n=8): control, LPS control (both control groups received olive oil) and three experimental groups treated with NS seeds oil in dose 1, 3 and 5 ml/kg bw. Animals were treated 3 weeks before the behavioral tests and throughout the experiment. LPS was injected intraperitoneally in dose 2 mg/kg bw at day 15. Step-through passive avoidance (STPA) task and novel object recognition test (NORT) were used to assess learning and memory processes. Latency time and recognition index (RI) were calculated, respectively. High performance liquid chromatography (HPLC) was used for quantitative determination of thymoquinone in the oil. One-way ANOVA was used to compare differences between groups (SPSS statistics19.0).

Results: The amount of the main active substance TQ is 21.37 ± 0.38 mg / ml in the used oil. Therefore, when rats were treated with oil doses of 1, 3 or 5 ml / kg bw, they received 21.37, 64.12 and 106.85 mg of TQ, respectively. These amounts correlate with those used by Mamun et al., who administered pure TQ to rats [3]. In STPA task rats from all groups increased latency time during the 2-day learning session. That was indicative for their ability to acquire the information. A significant decrease in latency and RI (p<0,05) was registered in LPS control in comparison to the control group which confirmed the memory-impairing effect of LPS administration. The animals treated with the highest dose of NS seeds oil insignificantly increased the latent time during the short-term memory test (on day 3) compared to LPS control. Significance (p<0,05) was reached during the long-term memory retention (on day 10). In NORT, the rats treated with 5 ml/kg bw NS seeds oil demonstrated considerable increase in RI in comparison with LPS control (p<0,05). We found no significant difference among NS seeds oil treated animals and control in terms of RI.

Conclusion: NS improves spatial working and episodic memory in hippocampal dependent memory tasks which is probably mediated by its active constituent thymoquinone. The latter was found in significant amount in the investigated oil.

References

[1]. Bin Sayeed, M.S., Asaduzzaman, M., Morshed, H., Hossain, M.M., Kadir, M.F., Rahman, M.R., 2013. The effect of Nigella sativa Linn. seed on memory, attention and cognition in healthy human volunteers. J. Ethnopharmacol. 148(3), 780-786. [2]. Hosseini, M., Mohammadpour, T., Karami, R., Rajaei, Z., Reza Sadeghnia, H., Soukhtanloo, M., 2015. Effects of the hydro-alcoholic extract of Nigella sativa on scopolamine-induced spatial memory impairment in rats and its possible mechanism. Chin. J. Integr. Med. 21(6), 438-444. [3]. Al Mamun, A., Matsuzaki, K., Islam, R., Hossain, S., Hossain, M.E., Katakura, M., Arai, H., Shido, O., Hashimoto, M., 2022. Chronic administration of thymoquinone enhances adult hippocampal neurogenesis and improves memory in rats via regulating the BDNF signaling pathway. Neurochem. Res. 47(4), 933-951. [4]. Anaeigoudari,