SHORT COMMUNICATION

Effects of ondansetron on social behaviour in male mice

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Background

The selective serotonin 5-HT3 receptor antagonist ondansetron is clinically used mainly to treat nausea and vomiting induced by chemotherapy. There are indications that it might be beneficial also in management of schizophrenia and alcoholism (Bennett & Vila 2010; Johnson 2010), however further studies are needed to elucidate the mechanisms involved and reveal other possible indications of ondansetron in clinics. Serotonergic neurotransmitter system plays a role in many central nervous functions, including those related to social behaviours such anxiety, fear and depression (Harmer *et al* 2006). In the present study, the aim was to assess the effect of repeated administration of ondansetron on behavioural profiles of singly-housed mice exposed to dyadic social interactions with non-aggressive group-housed male counterparts. The conspecific social conflict between a pair of adult male mice can be used as an ethological model for screening drugs for their behavioural effects (Krsiak 1975). In singly-housed male mice (isolates) during their interactions with non-aggressive group-housed partners the naturally occurring activities that can be characterised as sociable, defensive-escape (timid) or aggressive can be identified by ethological analysis, as well as the non-social activities such as ambulatory (locomotor) behaviours and rearing.

Methods

We used adult male mice of the albino ICR outbred strain (VELAZ s.r.o., Prague, Czech Republic). Animals were housed under constant light-dark cycle with lights on at 6.00 a.m. and off at 6:00 p.m. The animals (29–35 g) were randomly divided into two groups according to housing conditions. The mice housed in groups of 15–17 in standard plastic cages (38×22×14 cm) received no drug treatment. The other group (mouse isolates, n=62) were housed individually in self-cleaning cages (8×6×13 cm) for 21 days prior to behavioural testing that was performed during the light phase in the same room. On 22nd day each mouse isolate was administered with water orally and was transferred into the observational Plexiglas neutral cage (20×20×30 cm) with clean wooden shavings for 30 min adaptation period. Then the animal received a non-aggressive group-housed partner and their social interaction (control interaction) was video-recorded for 4 min. The frequencies of occurrence of the following behavioural elements were scored in the mouse isolates: sociable (following the partner, sniffing, climbing over the partner), timid (defence, escape, alert posture), aggressive (tail rattling, aggressive unrest, attack) agonistic activities and the locomotor parameters (walking, rearing). The behavioural data obtained from the singly-housed animals were subjected to the software system OBSERVER 3.1 (Noldus Information Technology b.v., Holland) used for further ethological and statistical analysis. The behavioural acts mentioned above were scored in the singly-housed individuals, while the non-aggressive group-housed partners served only as social stimuli for the mouse isolates. According to behavioural profiles during the initial 4-min agonistic interactions after water administration, we distinguished three behavioural types of

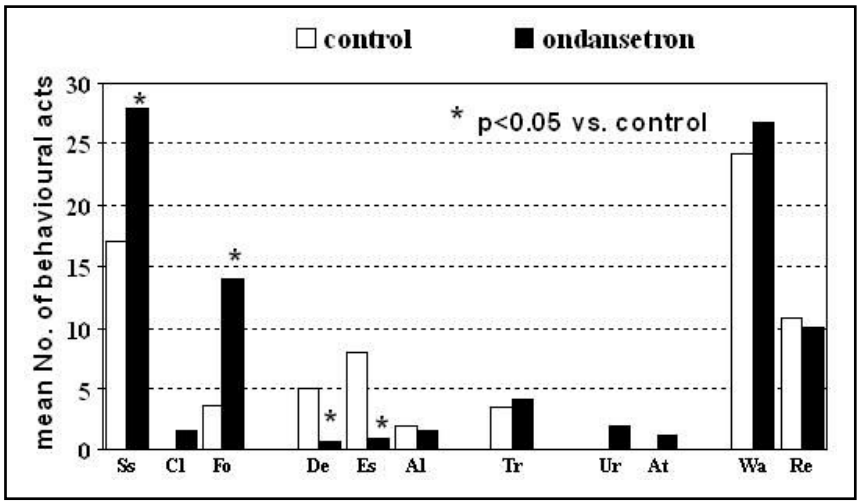

Fig. 1. Effect of ondansetron (1 µg/kg/day, orally for 21 days) on sociable (Ss, Cl, Fo), timid (De, Es, Al) and aggressive (Tr, Ur, At) behavioural elements and locomotor activities (Wa, Re) in singly-housed timid mice exposed to social interactions with non-aggressive group-housed partners. Ss – social sniffing, Cl – climbing, Fo – following the partner, De – defense, Es – escape, Al – alert posture, Tr – tail rattling, Ur – aggressive unrest, At – attack, Wa – walking, Re – rearing. Values represent mean frequencies. * $p<0.05$.

the subjects from individual housing. They were classified as a) aggressive (n=17), when at least one attack towards the non-aggressive partner occurred; b) timid (n=28), with pronounced defensive-escape behavioural elements and c) sociable (n=17), without attacks and with no defensive-escape activities (Pistovcakova & Sulcova 2002). They were randomly divided into two treatment groups with water administered as a control (10 ml/kg/day, orally), or ondansetron administered at the dose of 1 microgram/kg/day, orally in the same volume for three weeks. 24 hours after the last water/ondansetron administration the 4-min agonistic interaction of the singly-housed mouse with a non-aggressive group-housed mouse (the same partner as was in the previous behavioural testing) was performed using the same experimental conditions as described above (see the control interaction) and video-recorded for successive ethological analysis. Behavioural data subjected to the nonparametric Mann-Whitney statistical test were analysed separately for the timid, sociable and aggressive mice. The level of statistical significance was set at $p<0.05$. The study protocol was approved by the Animal Care Committee of the Masaryk University Brno, Faculty of Medicine, Czech Republic and carried out under the European Community guidelines for the use of experimental animals.

Results

In the singly-housed mice, which were in the control agonistic interaction classified as timid, ondansetron (1 microgram/kg/day, orally for 21 days) produced a significant ($p<0.05$) increase in the sociable behavioural acts such as sniffing and following the partner. Moreover, ondansetron significantly inhibited the frequencies of defences and escapes in the timid mice (***Fig. 1***). There were no significant antiaggressive effects induced by ondansetron in the aggressive group of isolates and neither there was any marked impact on behavioural profiles of the sociable group of mice (data not shown).

Conclusions

The behavioural data obtained indicate anxiolytic effect of ondansetron after its repeated administration. The explanation for this finding could be based on the fact, that 5-hydroxytryptamine (5-HT3) receptors are thought to participate in the stress-induced release of cortisol and adrenocorticotropin hormones (Patel *et al* 2011). The antagonistic action of ondansetron at 5-HT3 receptors could possibly reduce response to stress in timid mice. Present data add to ondansetron antidepressant-like effects described earlier in the model of depression induced in rats by bilateral olfactory bulbectomy (Pistovcakova *et al* 2010; Ramamoorthy *et al* 2008). Both, the anxiolytic and antidepressant potentials of ondansetron, that is often used in cancer patients following chemotherapy as the antiemetic agent, is a promising finding with regard to its potential psychotropic implications.

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