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SAVEZ FARMACEUTSKIH UDRUŽENJA SRBIJE

11000 Beograd, Bulevar vojvode Mišića 25, pošt. fah 664

tel/fax: + 381 11 2648 385; +381 11 2648 386

e-mail: fds@sbb.rs; sfus@farmacija.org

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NOVI POZITIVNI MODULATOR α4-GABAA RECEPTORA, XHE-III-74, SMANJUJE UNOS ALKOHOLA U MIŠIJEM MODELU „PIJENJA U MRAKU"

Tamara Stanković[1], Bojan Batinić[2], Anja Santrač[1], Bojan Marković[3], Milica Drobac[4], Jelena Arsenijević[4], Miroslav Savić[1]

[1]Katedra za farmakologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [2]Katedra za fiziologiju, Univerzitet u Beogradu - Farmaceutski fakultet, [3]Katedra za farmaceutsku hemiju, Univerzitet u Beogradu - Farmaceutski fakultet, [4]Katedra za farmakognoziju, Univerzitet u Beogradu - Farmaceutski fakultet (Srbija)

Cilj ove studije bio je da se ispita da li akutni tretman ligandom XHe-III-74, novim pozitivnim modulatorom α4-$GABA_A$ receptora, može smanjiti unos alkohola u mišijem modelu „pijenja u mraku" (eng. *drinking in the dark – DID*).

Eksperimenti su sprovedeni na odraslim miševima soja C57BL/6. Moguće sedativno dejstvo XHe-III-74 (0,5; 2 ili 5 mg/kg, i.p.) ispitano je u testu spontane lokomotorne aktivnosti (SLA). Prvog dana jednog ciklusa DID eksperimenta svaka životinja imala je dvočasovni pristup alkoholu (etanol 20%, v/v). Drugog dana tretman je primenjivan 20 minuta pre pristupa alkoholu, a trećeg dana pacovi nisu tretirani ničim. U svim DID eksperimentima svaka životinja je prošla kroz četiri ciklusa tako da je u svakom primila jednu od tri doze tretmana ili placebo. U prvom DID eksperimentu testirali smo efekat XHe-III-74 (0,8; 2 ili 5 mg/kg) na unos vode (n=12, po dozi), dok smo u drugom testirali efekat istih doza na unos alkohola (n=14). Ekekat referetnog leka, naltreksona (1; 4 ili 16 mg/kg) testiran je u trećem eksperimentu. U SLA testu, nijedna od odabranih doza XHe-III-74 nije smanjila pređeni put životinje ($F_{3,20}$=0,48; p=0,703). U prvom DID eksperiementu, tretman XHe-III-74 nije uticao na unos vode ($F_{3,33}$=0,39; p=0,763). Unos alkohola, meren u drugom DID eksperimentu, izmenjen je pod dejstvom XHe-III-74 tretmana ($F_{3,39}$=7,41; p<0,001), gde je doza XHe-III-74 od 5 mg/kg značajno smanjila unos u poređenju sa kontrolom (p<0,001). U trećem eksperimentu, naltrekson je značajno smanjio unos alkohola (F60,3=22.18; p<0,001), i to u sve tri doze: 1 mg/kg (p<0,001); 4 mg/kg (p<0,001) i 16 mg/kg (p<0,001).

Uz očekivani izostanak sedativnog dejstva, XHe-III-74, pozitivni modulator α4-$GABA_A$ receptora, ispoljio je evidentan potencijal za smanjenje unosa alkohola u mišijem DID modelu, koji se može porediti sa onim postignutim primenom naltreksona, referentnog leka u terapiji poremećaja unosa alkohola.

A NOVEL POSITIVE MODULATOR OF α4-GABAA RECEPTORS, XHE-III-74, REDUCES ETHANOL INTAKE IN MOUSE „DRINKING IN THE DARK" MODEL

Tamara Stanković[1], Bojan Batinić[2], Anja Santrač[1], Bojan Marković[3], Milica Drobac[4], Jelena Arsenijević[4], Miroslav Savić[1]

[1]Department of Pharmacology, Universitiy of Belgrade - Faculty of Pharmacy, [2]Department of Physiology, Universitiy of Belgrade - Faculty of Pharmacy, [3]Department of Pharmaceutical Chemistry, Universitiy of Belgrade - Faculty of Pharmacy, [4]Department of Pharmacognosy, Universitiy of Belgrade - Faculty of Pharmacy (Serbia)

The present study aimed to investigate whether acute treatment with XHe-III-74, a novel positive modulator of α4-$GABA_A$ receptors, may reduce alcohol intake in mouse model of „drinking in the dark" (DID).

All experiments were conducted on adult C57BL/6 mice. Potential sedative properties of XHe-III-74, (0.5, 2 or 5 mg/kg, i.p.) were assessed using spontaneous locomotor activity (SLA) test. On the 1st day of one DID cycle each animal had 2-h access to ethanol (20%, v/v), on the 2nd day treatment was given 20 min before the access to ethanol, while on the 3rd day the animal was not treated in any way. In all DID experiments each animal passed through four cycles and respectively receive one of three treatment doses or solvent in each cycle. In Experiment 1 we tested whether XHe-III-74 (0.8, 2 or 5 mg/kg) had any effects on water intake (n=12 per treatment dose), while in Experiment 2, the same doses were used to test potential decrease of ethanol intake (n=14). Effects of the reference drug, naltrexone (1; 4 and 16 mg/kg) were tested in Experiment 3 (n=21). In the SLA test, none of the selected XHe-III-74 doses decreased the distance traveled ($F_{3,20}$=0.48; p=0.703). In DID Experiment 1, XHe-III-74 treatment didn't affect water intake ($F_{33,3}$=0.39; p=0.763). Ethanol intake, measured in Experiment 2, was affected by XHe-III-74 treatment ($F_{39,3}$=7.41; p<0.001), with 5 mg/kg XHe-III-74 significantly reducing the intake relative to control (p<0.001). In Experiment 3, naltrexone significantly affected the intake of ethanol ($F_{60,3}$=22.18; p<0.001), with all three doses reducing the intake: 1 mg/kg (p<0.001); 4 mg/kg (p<0.001) and 16 mg/kg (p<0.001).

With expected lack of sedative actions, XHe-III-74, a positive modulator of α4-$GABA_A$Rs, exhibited a clear potential for decreasing ethanol intake in mouse DID model, comparable to that of naltrexone, a reference drug in alcohol use disorder.