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Exercise reduces nicotine withdrawal: Association with elevated hippocampal α7 nAChR

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Few attempts to quit smoking are successful, making current interventions relatively ineffective. Evidence shows that exercise decreases nicotine (NIC) withdrawal symptoms in humans (1), but the mechanism is unclear. In animals, exercise has been shown to reduce withdrawal from drugs such as morphine (2). This study aimed to explore the mechanisms underpinning the effect of exercise on NIC withdrawal severity.

Male C57Bl/6 mice (8 weeks) were surgically implanted with a subcutaneous minipump infusing NIC (24 mg/kg/day) or saline for 14 days, and underwent one of three concurrent exercise regimes (2x3 factorial design): 24 hrs/day (n=13), 2 hrs/day (n=12-14) and 0 hrs/day (n=12-13) running wheel access in their home cage. On day 14, withdrawal was precipitated by injection of mecamylamine (3 mg/kg, s.c.), a nicotinic receptor antagonist, and withdrawal symptoms were assessed (3) for 30 minutes. Quantitative autoradiography of brain sections was performed for α4β2 (4) and α7 (5) nicotinic receptors (nAChR), μ-opioid (MOPr; 6) and dopamine D_2 (7) receptors, brain-derived neurotrophic factor (BDNF) and plasma corticosterone. All procedures were performed in accordance with the Home Office Animal (Scientific Procedures) Act, 1986. Individual withdrawal symptoms were normalised to range between 0-100 and a composite total withdrawal factor calculated (withdrawal score units, WSU).

There was a significant effect of exercise and treatment on withdrawal (Two-way ANOVA test, $p<0.05$ and $p<0.001$, respectively). Nicotine-treated mice in the sedentary group displayed significantly higher severity of withdrawal symptoms (63.4±7.5 WSU) than mice in the 2 or 24 hrs/day wheel access groups (34.2±4.9 WSU; 39.8±4.9 WSU, respectively, both $p<0.01$). There was no difference in severity of withdrawal between 2 and 24 hrs/day wheel access groups. Two-way ANOVA of α7 nAChR binding (n=4-6) in CA1 and CA2/3 hippocampal regions found significant Exercise and Treatment effects (both $p<0.01$) and interactions in the CA2/3 only ($p<0.05$). Duncan's post-hoc found significantly higher levels of binding in the CA1 ($p<0.01$) and CA2/3 ($p<0.001$) of NIC-treated mice in the 2 (31.4±1.4 and 48.0±1.9 fmol/mg, respectively) and 24 hrs/day (31.0±1.7 and 40.3±1.3 fmol/mg, respectively) wheel access groups compared to 0 hrs/day (22.9±1.0 and 36.5±1.8 fmol/mg, respectively). There was also a NIC-induced increase in α7 binding in the basolateral amygdala compared to saline controls in all three exercise groups ($p<0.05$). NIC-treated mice displayed increased α4β2* nAChR binding ($p<0.001$) and plasma corticosterone levels ($p<0.01$), irrespective of exercise regime. MOPr binding was increased in the periaqueductal grey in mice undergoing 2 ($p<0.05$) and 24 hrs/day ($p<0.01$) compared to 0 hrs/day exercise. There were no significant effects of either NIC or exercise on D_2 receptors or BDNF.

These data provide first evidence that exercise attenuates nicotine withdrawal in mice, mirroring human studies where even a low level of exercise aids in reducing withdrawal symptoms, but a higher level of exercise does not provide greater benefit. Exercise affected nAChRs in a subtype and region-specific manner; therefore, exercise may attenuate nicotine withdrawal symptom severity through a hippocampal α7-receptor mediated mechanism.

(1) Haasova M, Warren FC, Ussher M et al (2013) Addiction 108:26 (2) Miladi-Gorji H, Rashidy-Pour A, Fathollahi Y (2012) Physiol Behav 105:195-202 (3) Castañé A, Valjent E, Ledent C et al (2002) Neuropharm 43:857 (5) Marks MJ, Whiteaker P, Grady SR et al (2002) J Neurochem, 81:1102 (6) Orr-Urtreger A, Goldner FM, Saeki M et al (1997) J Neurosci 17:9165-71 (7) Kitchen I, Slowe SJ, Matthes HW et al (1997) Brain Res 778:73 (8) Lena I, Matthes H, Kieffer B et al (2004) Neurosci Lett 356:220