Exercise Differentially Affects Nicotinic Receptor Subtypes To Attenuate Nicotine Withdrawal In Mice

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Less than 50 % of attempts to quit smoking are successful, making current interventions both expensive and relatively ineffective. Previous research has demonstrated that just 10 minutes of moderate intensity exercise could decrease nicotine withdrawal symptoms and cravings in humans (Ussher et al., 2012). In animals, exercise has been shown to attenuate self-administration of cocaine (Lynch et al. 2010), morphine (Hosseini et al., 2009) and alcohol (McMillan et al., 1995). This study aimed to explore the mechanisms underpinning the effect of exercise on nicotine withdrawal severity.

C57Bl/6 male mice (B&K Universal, UK) were surgically implanted with a subcutaneous minipump infusing nicotine (24 mg/kg/day) or saline for 14 days, and underwent one of three exercise regimes: 24 hrs/day, 2 hrs/day and 0 hrs/day running wheel access for 14 days 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 for 30 minutes (Damaj et al., 2003). Quantitative autoradiography of brain sections was performed for α4β2 (Besson et al., 2006; Marks et al., 2002) and α7 (Orr-Urtreger et al., 1997) nicotinic receptors. All procedures were performed in accordance with the Home Office Animal (Scientific Procedures) Act, 1986.

Individual withdrawal symptoms were normalised to range between 0 and 100 and a composite total withdrawal factor calculated (withdrawal score units, WSU; n = 10-11). There was a significant effect of exercise on withdrawal (Kruskal-Wallis test, $p<0.05$). Nicotine treated mice in the sedentary group displayed significantly higher severity of withdrawal symptoms (63.4±7.5 WSU) than mice in the 2 (34.2±4.9 WSU, $p<0.01$) or 24 hrs/day (39.8±4.9 WSU, $p<0.05$) wheel access groups There was no difference in severity of withdrawal between 2 and 24 hrs/day wheel access groups. Two-way ANOVA followed by Duncan's post-hoc analysis of quantitative autoradiography (n = 4-6) found a significant increase in α7 nicotinic receptor binding in CA1 ($p<0.01$) and CA2/3 ($p<0.001$) hippocampal regions in nicotine-treated mice in the 2 (31.4±1.4 and 48.0±1.9 fmol/mg, repsectively) 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 nicotine-induced increase in α7 binding in the basolateral amygdala compared to saline controls in all three exercise groups ($p<0.05$, see table). However, there was no effect of exercise on α4β2 nicotinic receptor binding.

	α7 nicotinic receptor binding in the basolateral amygdala (fmol/mg)		
	Wheel access group		
Treatment	0 hrs/day	2 hrs/day	24 hrs/day

Saline	23.9±1.0	22.8±1.3	24.7±1.7
Nicotine	29.5±1.1 *	28.3±2.3 *	31.3±1.3 *

*p<0.05 vs saline controls

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 necessarily provide greater benefit. Exercise also differentially affects nicotinic receptor subtypes in a region-specific manner, increasing α7 binding levels in the hippocampus of nicotine withdrawn exercising animals. Therefore, exercise may attenuate nicotine withdrawal through an α7-receptor mediated mechanism.

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