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## Dose, duration, and pattern of nicotine administration as determinants of behavioral dependence in rats

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Unfortunately, the author's corrections to two pages of the proof were not carried out. The correct sentences are given here.

Within Results, the last section should begin as follows:

### Required patterns of exposure for dependence

The response rate data for the rats that were administered a 24-h nicotine-free period after 1 day of nicotine administration are shown in Fig. 5a (Group NIC-1D).

Within Discussion, the third paragraph should read as follows:

Withdrawal effects (response rate reductions) were observed after mecamylamine challenges across a range of nicotine doses (3, 6, and 12 mg kg<sup>-1</sup> day<sup>-1</sup>) and at different durations of exposure (7 and 12 days of administration). In addition, it was found that, at the highest dose of nicotine administration, 12 mg kg<sup>-1</sup> day<sup>-1</sup>, mecamylamine-precipitated withdrawal effects were observed after 7 days, but not after 12 days, of continuous nicotine administration. This is unlike the results obtained in the lower dose groups where withdrawal effects were observed on both days 7 and 12. For the inability to precipitate withdrawal in the 12 mg kg<sup>-1</sup> day<sup>-1</sup> dosage group on day 12 could possibly be due to insurmountably high levels of nicotine at the nAChRs. Thus, it could be suggested that with a large daily dose

of nicotine, such as 12 mg kg<sup>-1</sup> day<sup>-1</sup>, mecamylamine challenges at the dose administered may have insufficiently blocked the nAChRs, and subsequent withdrawal effects were less likely to be observed.

Within Discussion, the fifth paragraph should read as follows:

Patterns of nicotine intake have been suggested as important determinants for the induction of nicotine dependence in laboratory animals. For example, nicotine withdrawal, as measured by somatic signs of withdrawal and increases in brain reward thresholds, has been shown to vary with daily dose, duration of delivery, and exposure patterns (intermittent vs continuous) (Skjei and Markou 2003), and magnitude of withdrawal has been suggested to be positively related to nicotine exposure (Malin et al. 1992; Skjei and Markou 2003). In experiment 2, it was demonstrated that by inserting a 24-h nicotine-free period after the third day of a seven day cumulative regimen of nicotine administration, disruptions of operant behavior were observed that were similar to those following mecamylamine challenges after 7 days of continuous nicotine administration in experiment 1. It is unknown whether dependence was induced from the final 4 days of nicotine exposure or if dependence was induced through a combined exposure including one or more of the nicotine days administered prior to the nicotine-free period. Taken together, these findings underscore important issues such as minimal number of days of nicotine administration necessary to induce dependence and whether nicotine dependence may be affected by nicotine-free periods.

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