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LB-102 effect on dopamine D₂ autoreceptors: Results from a preclinical study evaluating dopamine efflux in rat nucleus accumbens using microdialysis

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Background

- LB-102 is an investigational novel benzamide D₂/D₃/5-HT₇ receptor antagonist under development as a once-daily treatment without titration for schizophrenia, bipolar depression, adjunctive treatment of major depressive disorder, and other neuropsychiatric disorders.^{1,2}
- Because presynaptic dopamine D₂/D₃ autoreceptors exert powerful inhibitory control over dopamine synthesis, release, and extracellular availability,³ compounds that antagonize these receptors may modulate mesolimbic dopamine signalling in a therapeutically meaningful manner.^{4,5}
- The nucleus accumbens (NAc), a key mesolimbic dopamine projection region in the brain involved in reward and motivation, is implicated in schizophrenia, depression, and related disorders that are characterised by anhedonia and motivational deficits.^{6,7}
- In vivo* microdialysis provides a functional assay of presynaptic D₂ autoreceptor activity by measuring the ability of a candidate compound to reverse inhibition of dopamine efflux elicited by quinpirole, a D₂ autoreceptor agonist.^{8,9}

Objective

- To determine whether orally administered LB-102 affects basal dopamine efflux in the NAc in freely moving rats and to test the hypothesis that LB-102 reverses presynaptic D₂ autoreceptor-mediated inhibition of dopamine efflux in the NAc. In this regard, this preclinical mechanistic study examines whether LB-102 increases dopamine release in the NAc, the brain's key reward and motivation circuit, by reversing autoreceptor-mediated inhibition, an effect that could help address the dopamine deficits driving anhedonia and low motivation in depression.

Methods

Experimental design

- Male Sprague-Dawley rats were implanted with bilateral guide cannulae targeting the NAc and studied using *in vivo* microdialysis with high-pressure liquid chromatography/electrochemical detection for dopamine quantification.
- After stabilisation, extracellular dopamine was sampled at 10-minute intervals and normalised to each animal's pretreatment baseline.
- Rats were randomly assigned to receive treatment in Experiment 1 or Experiment 2:
 - Experiment 1:** Rats received LB-102 by oral gavage at 1.5, 3.0, or 6.0 mg/kg, and dopamine efflux was monitored for 180 minutes.
 - Experiment 2:** Quinpirole (0.1 µM) was infused locally into the NAc by reverse microdialysis over a 3-hour duration to suppress dopamine efflux. LB-102 (1.5, 3.0, or 6.0 mg/kg) or vehicle was administered by oral gavage 30 minutes after initiation of quinpirole infusion, and dopamine sampling continued for up to 3 hours.

Data presentation and analysis

- Treatment effects were quantified as area-under-the-curve (AUC) of baseline-normalised responses.
- One-sample t-tests assessed within-group effects, and one-way ANOVA followed by Dunnett's or Tukey's multiple-comparison testing evaluated between-group comparisons.
- Probe placements were histologically verified.

Results

Experiment 1

- All doses of LB-102 administered orally in the absence of quinpirole produced a moderate and sustained increase in dopamine efflux in the NAc (mean elevations: ~10-15% above baseline across doses tested) (**Figure 1A**).
- Changes in dopamine efflux were significantly greater with LB-102 6.0 mg/kg compared to baseline (one-sample t-test: $t[11]=2.66$; $p=0.022$) (**Figure 1B**).
- Between-group comparisons demonstrated that LB-102 dose did not have a significant effect on AUC values (one-way ANOVA: $F[2,27]=0.064$; $p=0.94$).

Experiment 2

- Local infusion of quinpirole by reverse microdialysis in the NAc produced a marked and sustained decrease in dopamine efflux in the NAc to ~65% of baseline, confirming robust D₂ autoreceptor-mediated suppression (**Figure 2A**).
- All doses of LB-102 administered orally 30 minutes after quinpirole gradually reversed the quinpirole-reduced dopamine efflux toward baseline over the course of the study (**Figure 2A**).
- Administration of vehicle by oral gavage produces a small transient change in dopamine efflux, typically in the range of ~5-10% increase from baseline levels.
- LB-102 treatment showed a dose-dependent trend toward a main effect on dopamine levels (one-way ANOVA: $F[3,37]=2.623$; $p=0.06$), with significantly greater changes in dopamine efflux seen with LB-102 6.0 mg/kg than with vehicle (Dunnett's test: $p=0.038$) (**Figure 2B**).

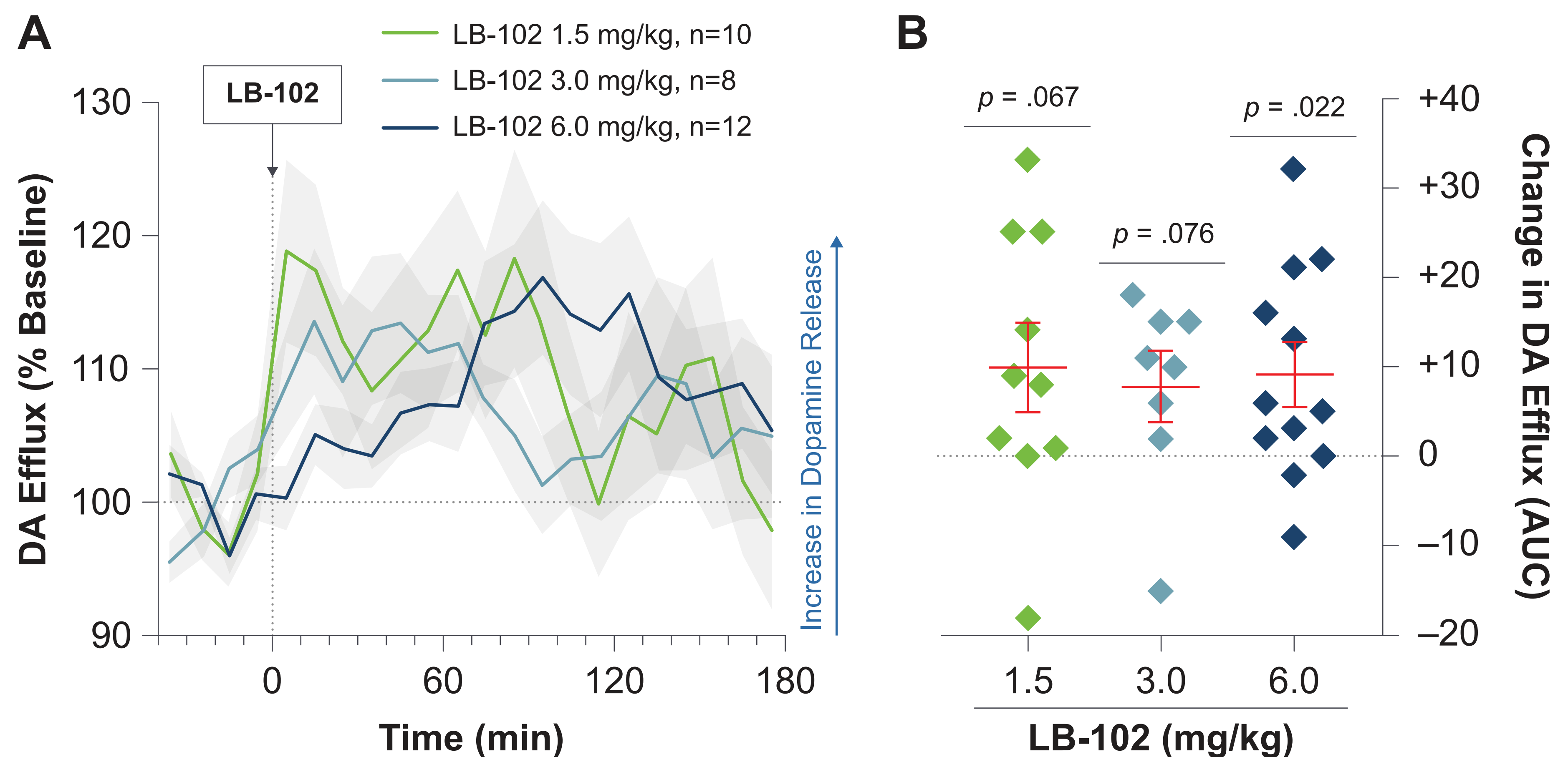
Location of microdialysis probes

- Histological verification demonstrated that microdialysis probes were localized to the shell/core border of the NAc (**Figure 3A**) and remained in the brain for less than 24 hours with minimal tissue damage (**Figure 3B**).
- Basal dopamine concentrations in microdialysis samples collected from the NAc ranged from 0.82 nM to 1.82 nM.

Behavioural observations

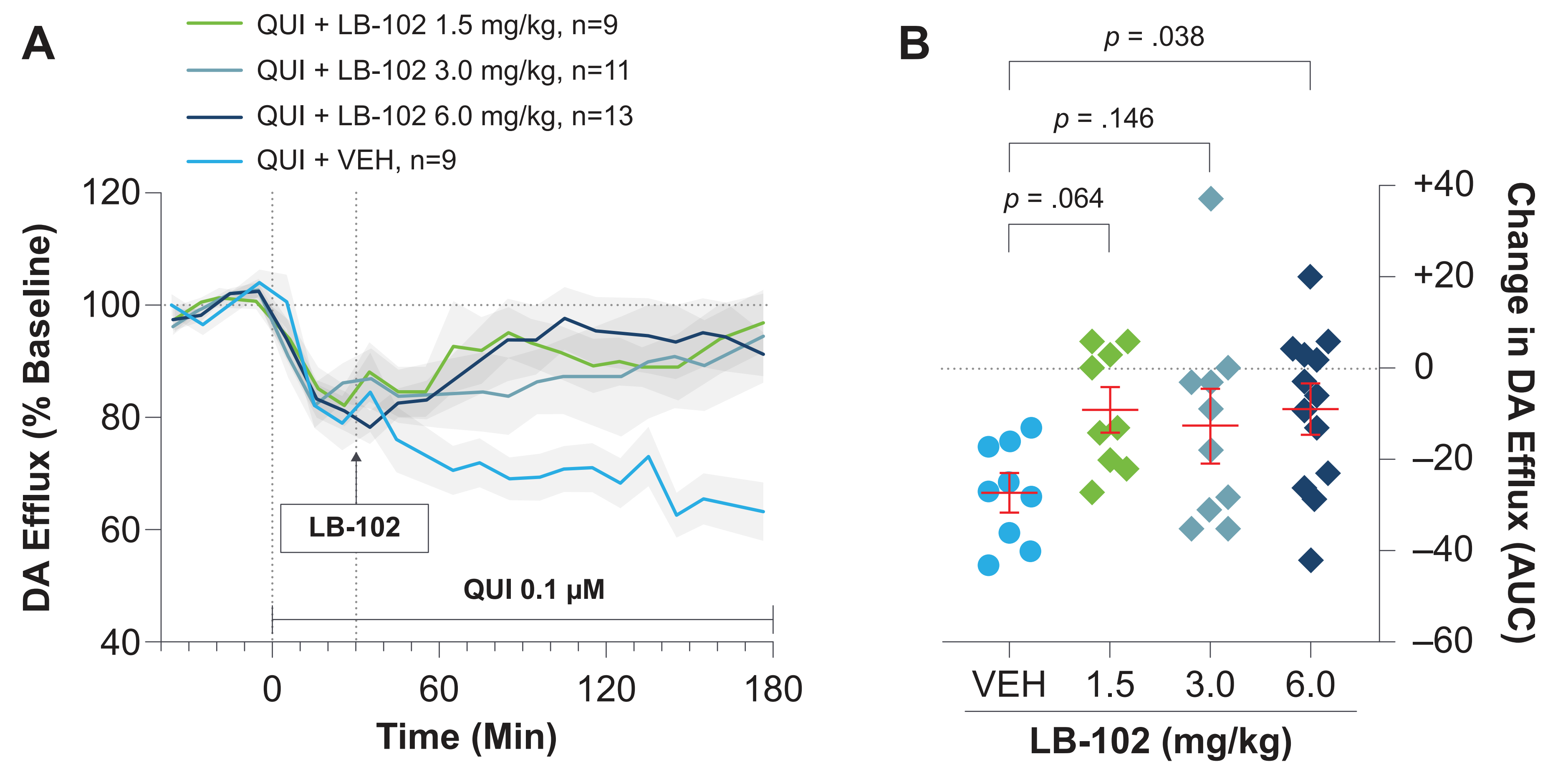
- Though not systematically measured, informal behavioural observations suggested increased arousal and exploration after administration of LB-102 at all doses.

Figure 1. Effect of Oral LB-102 on Dopamine Efflux in the NAc



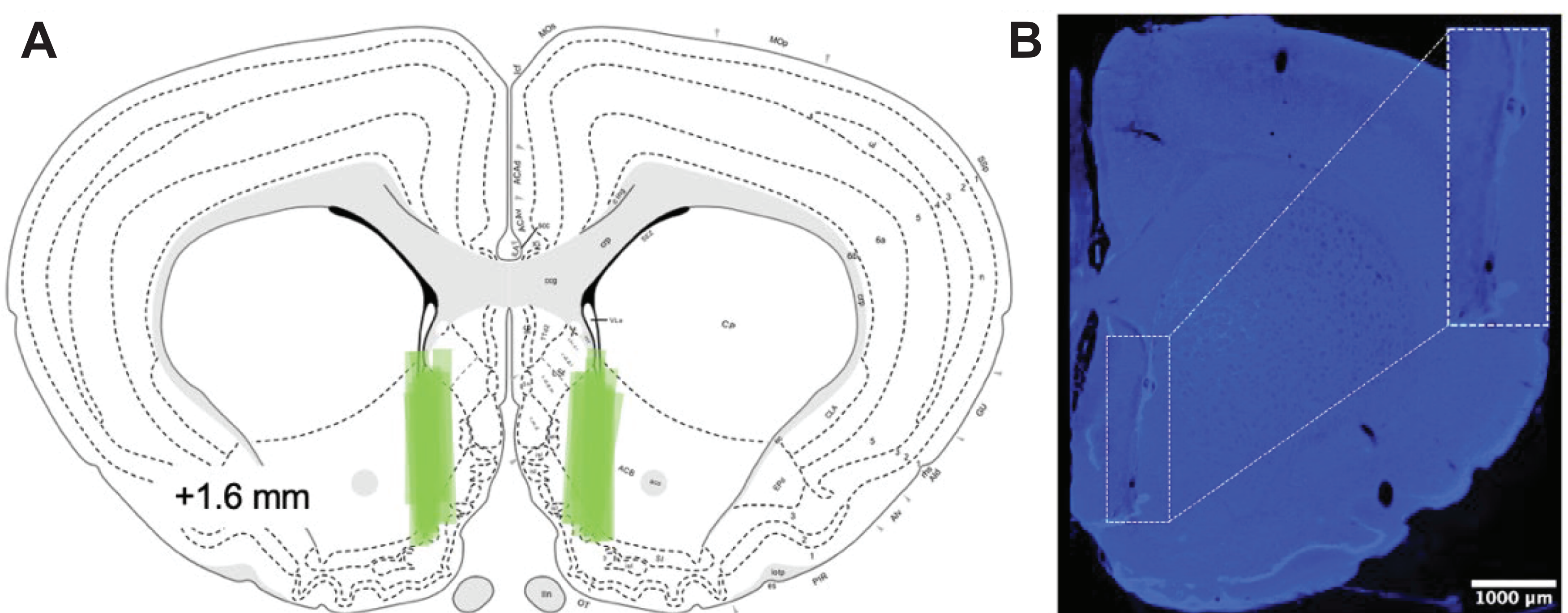
A: Time-course of dopamine efflux in the NAc following oral gavage of LB-102 at 1.5, 3.0 or 6.0 mg/kg. Data are expressed as the percentage of baseline and shown as mean ± SEM. The horizontal dotted line indicates 100% baseline, and the vertical dotted line indicates time of LB-102 treatment. B: Change in dopamine efflux in response to LB-102. Data are expressed as AUC over 0-180 min following treatment, with individual data shown as symbols and mean ± SEM in red. The dotted line indicates 0 change from baseline. Horizontal bars indicate one-sample t-test comparisons (vs baseline). AUC, area under the curve; DA, dopamine; NAc, nucleus accumbens; SEM, standard error of the mean.

Figure 2. Effect of Oral LB-102 on Quinpirole-Induced Suppression of Dopamine Efflux



A: Time-course of dopamine efflux during intra-NAc reverse-dialysis of quinpirole at 0.1 µM (over 0-180 min), followed by oral gavage of LB-102 at 1.5, 3.0 or 6.0 mg/kg. Data are expressed as percentage of baseline and shown as mean ± SEM. The horizontal dotted line indicates 100% baseline. The first and second vertical dotted lines indicate time of first treatment with quinpirole and LB-102, respectively. B: Change in dopamine efflux in response to LB-102 treatment. Data are expressed as AUC over 30-180 min following treatment, with individual data shown as symbols and mean ± SEM in red. The dotted line indicates 0 change from baseline. Horizontal brackets indicate Dunnett's test comparisons. AUC, area under the curve; DA, dopamine; NAc, nucleus accumbens; QUI, quinpirole; SEM, standard error of the mean; VEH, vehicle.

Figure 3. Location of Tracks Formed by Microdialysis Probes in the NAc



A: Vertical green lines represent the 2-mm length of the dialysis membrane at 1.6 mm anterior to bregma. Drawing of the coronal section was adapted from Paxinos and Watson (1997).¹⁰ B: A representative coronal slice imaged with DAPI staining and fluorescence microscopy showing the tract left by the probe membrane. The inset highlights minimal tissue damage associated with the probe. NAc, nucleus accumbens.

CONCLUSION

- These findings show that LB-102 reverses the quinpirole-induced reduction of dopamine efflux in the NAc of freely moving rats assessed with *in vivo* microdialysis, and support the hypothesis that LB-102 modulates mesolimbic dopaminergic signalling by functionally interfering with the presynaptic D₂ autoreceptor inhibitory activity.

DISCUSSION

- These data demonstrate that LB-102 enhances dopamine efflux in the brain by attenuating inhibitory signalling through dopamine autoreceptors that physiologically constrain dopamine release.
- By attenuating autoreceptor-mediated inhibition of dopamine efflux, LB-102 promotes increased dopamine neurotransmission, potentially addressing the hypodopaminergic state associated with anhedonia and diminished motivation in depression.
- This proposed mechanism is under active investigation across preclinical and clinical studies to further evaluate the efficacy of LB-102 in the treatment of depressive symptoms, including in an ongoing phase 2 trial for the treatment of bipolar depression (see [ECNP poster EP01-1056](#)) and a planned phase 2 trial for adjunctive treatment in major depressive disorder.

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GN, GS, and RS are employees and shareholders of LB Pharmaceuticals. SA holds a Research Associate position at the University of British Columbia and is a fractional employee of Resilience Biosciences Inc. AGP is Full Professor in the Department of Psychiatry at the University of British Columbia and has a non-salaried position as President and CEO of Resilience Biosciences Inc. AE was an employee and shareholder of LB Pharmaceuticals at the time of data analysis and abstract submission and was advisor of LB Pharmaceuticals during poster development.