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Nicotinamide adenine dinucleotide supplementation fails to enhance anesthetic recovery in rodents

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Nicotinamide Adenine Dinucleotide (NAD^+) is implicated in bioenergetics, DNA repair, and senescence. Depletion of NAD^+ is associated with aging and neurodegenerative disease, prompting a growing interest in NAD^+ supplementation. With rising over-the-counter use of NAD, understanding their impact on anesthetic recovery becomes essential. This study investigates the effect of NADH, a common NAD^+ precursor, on anesthesia in rodents. Baseline and post-anesthesia (1.5% isoflurane) open field and Y-maze activity were recorded in adult male and female C57BL/6 mice ($n = 8–10$/group). NADH (150 mg/kg, intraperitoneal) or vehicle (0.9% normal saline) were given at baseline or during anesthesia. The NADH-treated group exhibited a significant decrease in open-field activity relative to vehicle-treated. This diminished activity was reflected in reduced distance travelled and average velocity after emergence from anesthesia in the NADH-treated group. NADH treatment did not improve Y-maze performance after anesthesia, partly related to reduced locomotor activity in the NADH-treated group. This study demonstrates that NADH does not appear to hasten recovery from anesthesia. Instead, there was a depression in open-field activity and no change in Y-maze performance with NADH supplementation, indicators of locomotive and cognitive recovery in rodents. The broad implications of NAD^+ in aging are likely to shape supplementation trends, highlighting the importance of understanding the potential influence of administering NAD^+ on anesthetic sensitivity and recovery.

Nicotinamide Adenine Dinucleotide (NAD^+) is a critical coenzyme within all living cells regulating cellular bioenergetics, DNA repair, senescence, cell signalling, and mitochondrial homeostasis. NAD^+ serves as an electron carrier in metabolic pathways such as glycolysis, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. It alternates between oxidized and reduced forms to facilitate the transfer of electrons, which is essential for generating the cell's main energy currency. Interestingly, NAD^+ depletion is associated with normal and premature aging[1–3] and supplementation of NAD^+ precursors reverses mitochondrial dysfunction and extends the life span for wild-type mice and mice with premature aging[4,5]. These findings highlight the importance of NAD^+ in maintaining cellular and metabolic homeostasis.

Anesthetics are known to alter cerebral energy metabolism[6,7], suggesting that pathways involving NAD may be relevant in understanding anesthetic effects on neurologic function. As such, NAD^+ and its precursors, including NADH, have drawn interest for their potential effects on brain health. While the popularity of NAD supplementation has grown, with over-the-counter products marketed for supporting aging-related cognitive health, the biological consequences of such supplementation remain under investigation.

Neurocognitive performance after surgeries is a major concern as postoperative delirium affects 20–50% of patients after a major surgery[8,9] and exerts substantial repercussions on a patient's trajectory for recovery. Postoperative delirium is also linked to functional decline, prolonged hospitalization, institutionalization, and increased morbidity and mortality[9–18]. Thus, postoperative delirium underscores a significant clinical challenge. The treatment of post-operative delirium largely relies on risk-reductive strategies, including the avoidance of polypharmacy[19], pre-operative pain control[20,21], and avoiding prolonged fluid fasting[22]. However, few intraoperative interventions are effective against postoperative delirium[23]. Given the relative lack of interventions available to prevent delirium after surgery, an acute treatment given prior to emergence of anesthesia would be very appealing.

Given the link between NAD pathways and cerebral metabolism, understanding whether acute administration of NAD + precursors can influence the brain under anesthesia is of scientific interest. This study aims to investigate whether NADH, a widely available supplement, impacts recovery from general anesthesia in rodents. By exploring the effects of acute NADH administration, we seek to provide insights into its role in modulating neurocognitive recovery from anesthesia.

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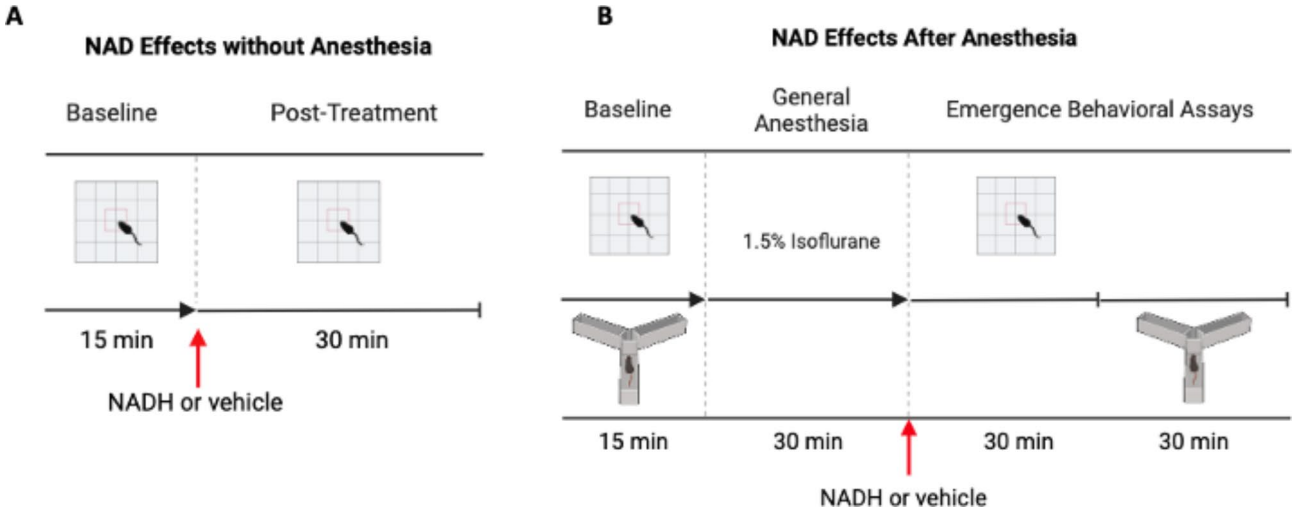

Fig. 1. Experimental protocols. (**A**) After collection of baseline open-field data, NADH (150 mg/kg, intraperitoneal) or 0.9% normal saline vehicle (0.1 mL, intraperitoneal) were given. Mice were returned for open-field observation for 30 min after treatment. (**B**) To determine the impact of NAD supplementation on general anesthesia, baseline open-field and Y-maze activity were recorded. Mice were then anesthetized for 30 min with 1.5% isoflurane. Just prior to emergence, mice were treated with NADH (150 mg/kg, intraperitoneal) or 0.9% normal saline vehicle (0.1 mL, intraperitoneal). After the return of the righting reflex, open-field and Y-maze were separately recorded for 30 min to assess anesthetic emergence activity.

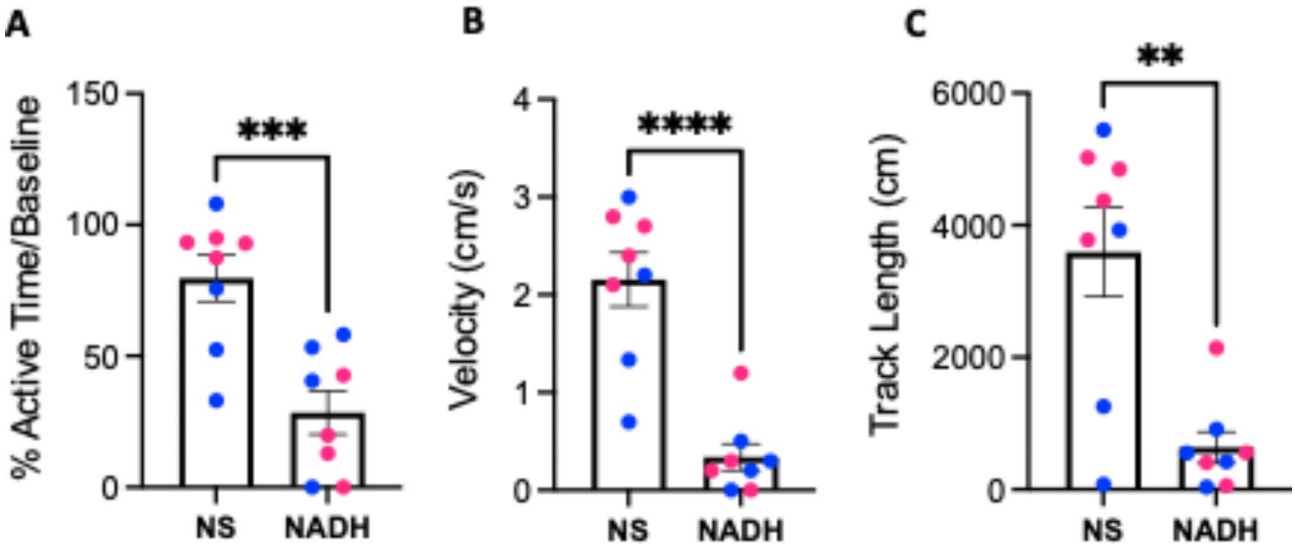

Fig. 2. Impact of NADH on rodent activity without anesthesia. (**A**) The percent time active for vehicle or NADH treated groups normalized to the pre-treatment baseline activity. (**B**) The average velocity (cm/s) of vehicle or NADH treated activity in an open-field averaged over 30 min. (**C**) The total track length (cm) travelled in the open-field for 30 min after treatment with vehicle or NADH. All male mice are labelled in blue and female in pink. NADH; nicotinamide adenine dinucleotide hydrogen, IP; intraperitoneal. $n = 8$/group. $^{**}p < 0.01$, $^{***}p < 0.005$, $^{****}p < 0.001$, student's t-test.

Results

A total of 52 rodents were used for the study (Fig. 1). All rodents were included in the study and no rodents were excluded from data analysis. There were no rodent mortalities from this study. All data generated and analyzed during this study are included in this manuscript and are available from the corresponding author on reasonable request.

NADH slows open-field behavior at baseline

Without anesthesia, NADH slows open-field behavior in C57/BL6 mice (Fig. 2). NADH significantly decreased the active time in an open field for at least 30 min compared to vehicle (Figs. 2A and 28.4 ± 8%*** vs. 79.7 ± 9%,

respectively, $n = 8$ per group; $^{***}p < 0.005$ vs. control). This was also reflected by reduced velocity travelled by the NADH treated group compared to vehicle (Fig. 2B, 0.34 ± 0.1 cm/s**** vs. 2.15 ± 0.3 cm/s, respectively, $n = 8$ per group; $^{****}p < 0.001$ vs. control) and total track length (Figs. 2C and 636.5 ± 237 cm** vs. 3591 ± 676 cm, respectively, $n = 8$ per group; $^{**}p < 0.01$ vs. vehicle).

NADH slows open-field behavior after emergence from general anesthesia

Open field behavior after emergence from general anesthesia was quantified. In addition, representative open-field tracking images in the vehicle and NADH treated mice after the emergence of anesthesia were obtained (Fig. 3A,B). After emergence from anesthesia, the NADH treated group was less active compared to vehicle (Fig. 3C). There was no significant difference between any of the baseline open-field characteristics prior to either anesthesia or treatment with vehicle or NADH (Fig. 3D–F). When normalized to baseline open-field activity, the NADH treated group was significantly less active compared to vehicle in the 30 min following emergence from general anesthesia (Figs. 3G and 24.4 ± 7 cm/s** vs. 61.4 ± 6 cm/s, respectively, $n = 8$ per group; $^{**}p < 0.01$). The distance travelled and the average velocity were significantly decreased in the NADH treated group after emergence (Fig. 3H and I, distance travelled: 946 ± 448 cm* vs. 2501 ± 325 cm, and average velocity: 0.52 ± 0.25 cm/s* vs. 1.39 ± 0.18 cm/s, $n = 8$ per group, $^{*}p < 0.05$). NADH treatment did not affect emergence, as the time to regain the righting reflex was no different between the NADH treated or vehicle untreated groups (Figs. 3J and 4.9 ± min vs. 4.0 ± min, respectively, $n = 8$ per group).

Acute NADH does not enhance Y-maze performance after anesthesia

The number of visits to the novel arm was significantly decreased in the NADH treated group after emergence from anesthesia when compared to number of visits prior to anesthetic administration (Fig. 4A, NADH group: 11 ± 3*** vs. 34 ± 5, respectively, $n = 10$ per group, $^{***}p < 0.005$). In contrast, there was no effect of anesthesia on the novel arm visits in the vehicle-treated group when comparing number of visits after emergence with respect to number of visits prior to anesthetic administration (Fig. 4A, vehicle group: 25 ± 3 vs. 24 ± 3, respectively, $n = 10$ per group). There was no significance difference between novel arm visits at baseline between vehicle and NADH treated groups. The number of visits to the alternate arm were also significantly decreased after anesthesia in the NADH treated group as compared to prior to anesthesia, but there was no difference in alternate arm visits between the NADH and vehicle treated groups after anesthesia (Fig. 4B, NADH group: 20 ± 3 vs. 6 ± 2***, respectively, vehicle group: 10 ± 2 vs. 14 ± 2, $n = 10$ per group, $^{***}p < 0.005$). Although there were fewer novel arm visits in the NADH treated group, there was no significant difference in the novel arm visit duration between NADH and vehicle before or after the anesthetic (Fig. 4C, NADH group: 248 ± 33 s vs. 255 ± 69 s, vehicle group: 278 ± 16 s vs. 268 ± 30 s, $n = 10$ per group). However, there were significantly less total arm entries in the NADH group after emergence from anesthesia compared to baseline (Fig. 4D, NADH group: 54.5 ± 5 vs. 17.2 ± 5****, vehicle group 39.1 ± 4 vs. 34.5 ± 4, $n = 10$ per group). The number of novel arm visits normalized to the total number of arm entries was not significantly different between treatment groups or with anesthesia exposure (Fig. 4E). Similar to the open-field activity, the NADH treated mice had a slower average velocity participating in the Y-maze as compared to vehicle treated mice after anesthesia (Fig. 4F, 2.6 ± 0.5*cm/s vs. 3.9 ± 0.3 cm/s, respectively, $n = 10$ per group, $^{*}p < 0.05$).

Discussion

Aside from using NAD + in the prevention and treatment of Alzheimers Disease and other forms of dementia[6], there is a newfound interest in using NAD + to prevent post-operative delirium. However, we find that NADH, a common over-the-counter supplement in adults, decreases the activity of rodents alone and following the emergence from general anesthesia. This was reflected by a decrease in open-field velocity, track length, and percent active time in mice that received NADH. NADH decreased both the number of novel arm visits and total arm entries in a post-anesthesia Y-maze trial compared to baseline. NADH treatment did not enhance Y-maze performance after exposure to isoflurane, which may be related to the impaired locomotor activity due to NADH. To our knowledge, this is the first study to demonstrate that acute NADH administration slows activity in rodents both at baseline and after isoflurane-induced general anesthesia.

NAD^+ depletion is a hallmark feature of normal aging and in neurodegenerative diseases, including Parkinson's and Alzheimer's diseases[2,24,25]. Therefore, the use of NAD^+ and its precursors, including NADH, have garnered significant attention for its potential to minimize the impact of brain aging. Zhu et al. showed that there is an age-dependent decrease in NAD + in the brains of healthy adults[3], which was in agreement with the observed age-dependent reduction of NAD + in the hippocampus of aged mice[26]. The age-related reduction in NAD + may be related to increased consumption by Poly (ADP-ribose) polymerase (PARPs) and CD38, which is in parallel with mitochondrial dysfunction in a sirtuin-dependent manner[2,27]. Importantly, NAD^+ augmentation increases resistance to oxidative stress, increases neurogenesis, and improves neuronal plasticity and cognitive function in aged rodent models[4,28]. The broad implications for NAD^+ and its role in healthy and pathologic aging have a major impact on NAD^+ supplementation in the adult population. It is important to recognize the potential impact NAD^+ has on recovery after anesthesia given its close link to neuronal plasticity and bioenergetics.

This study showed that the open-field activity, an indicator of locomotive recovery in rodents[29], was slowed in rodents receiving acute NADH administration relative to vehicle. There was no difference in Y-maze performance between NADH or vehicle treated mice after emergence from anesthesia. Interestingly, an acute dose of NADH suppressed open-field activity at baseline even without exposure to an anesthetic. We chose NADH as an NAD^+ precursor since it is a common and commercially available supplement, however there may be perturbations in the brain NADH redox state with acute NADH administration that effect cerebral blood flow and metabolic stress in the brain[30,31]. Future studies on the brain redox state with acute administration of NADH and additional NAD^+ precursors may shed light on the acute effects of NAD supplementation, with and without exposure

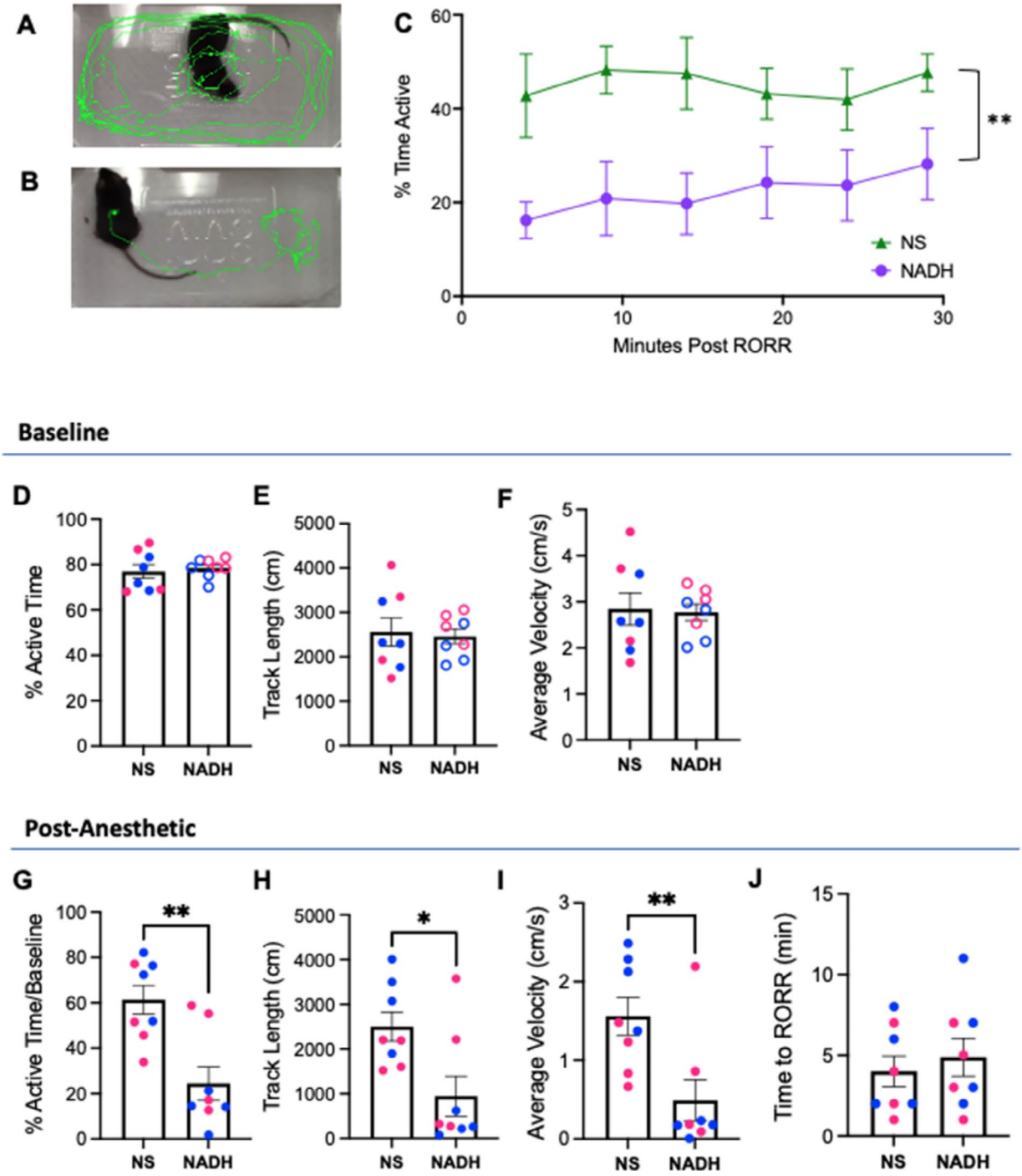

Fig. 3. Impact of NADH on post-anesthetic rodent activity (**A** and **B**) Representative open-field tracking images for the first two minutes after emergence from anesthesia in (**A**) vehicle and (**B**) NADH-treated mice. (**C**) Time course representing the percent time that the vehicle treated or NADH treated mice were active in an open-field for 30 min after the emergence of anesthesia. (**D**) The baseline (pre-anesthetic) percent active time in each group prior to vehicle or NADH treatment. (**E**) The total track length (cm) travelled in the open-field for 15 min at baseline (pre-anesthetic) in each group prior to vehicle or NADH treatment. (**F**) The average velocity (cm/s) in open-field at baseline (pre-anesthetic) in each group prior to vehicle or NADH treatment. (**G**) The percent active time normalized to the pre-anesthetic baseline activity in vehicle or NADH treated groups averaged over the first 15 min. (**H**) The total track length (cm) travelled in the open-field for 30 min after treatment with vehicle or NADH. (**I**) The average velocity (cm/s) of vehicle or NADH treated activity in an open-field averaged over 30 min. (**J**) The time to regain the righting reflex after discontinuation of isoflurane. All male mice are labelled in blue and female in pink. NADH; nicotinamide adenine dinucleotide hydrogen, IP; intraperitoneal, RORR; return of righting reflex. $n = 8$/group. $^{*}p < 0.05$, $^{**}p < 0.01$, one-way ANOVA (**C**), two-way ANOVA (**D**–**I**), or student's t-test (**J**).

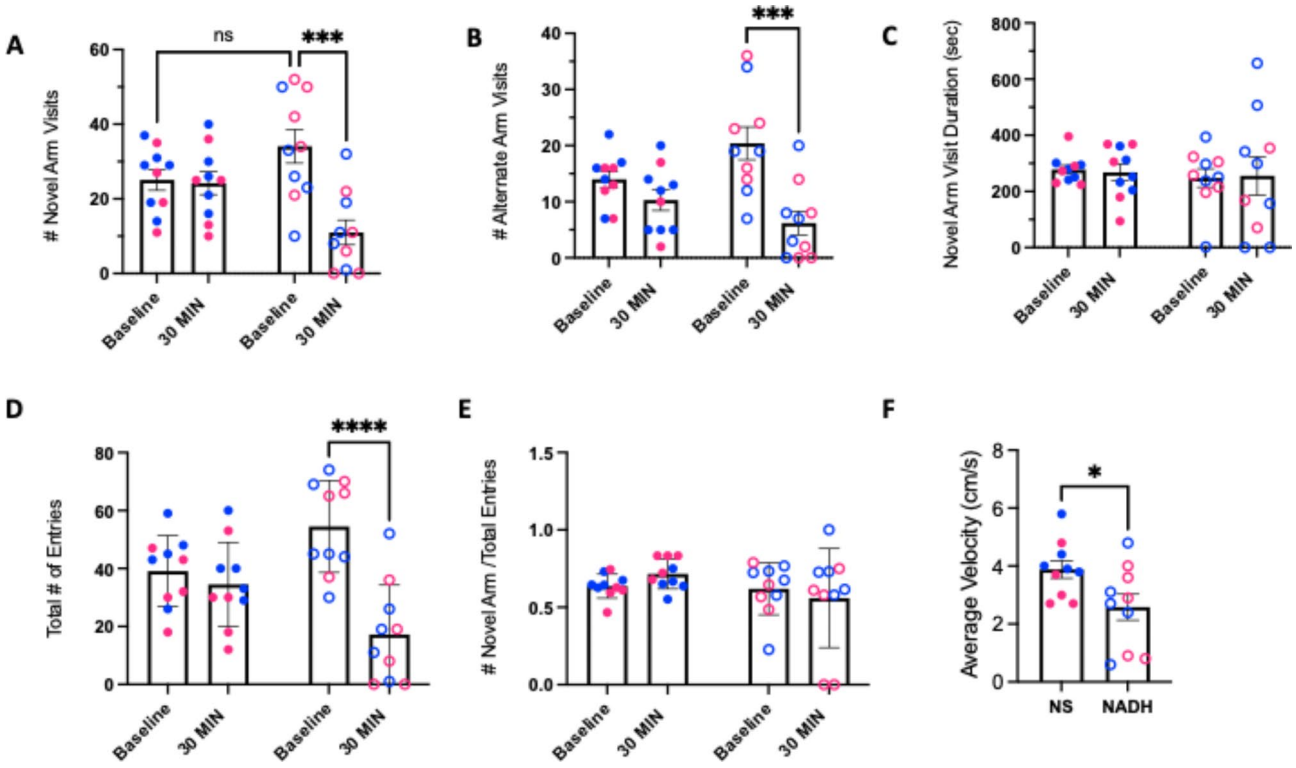

Fig. 4. No Impact of NADH on post-anesthetic short-term spatial memory in rodents. (**A**) The number of visits to the novel arm of the Y-maze at baseline and 30 min after emergence from general anesthesia in vehicle and NADH treated groups. (**B**) The number of visits to the alternate arm at baseline and 30 min after emergence from general anesthesia in vehicle and NADH treated groups. (**C**) The total duration spent in the novel arm at baseline and 30 min after emergence from general anesthesia in vehicle and NADH treated groups. (**D**) The total number of arm entries at baseline and 30 min after emergence from general anesthesia in vehicle and NADH treated groups. (**E**) The number of novel arm visits at baseline and 30 min after emergence from general anesthesia in vehicle and NADH treated groups normalized to the total number of arm entries during the trial. (**F**) The average velocity in all arms of the Y-maze for the duration of the experiment 30 min after emergence from general anesthesia in vehicle and NADH treated groups. All male mice are labelled in blue and female in pink. NADH; nicotinamide adenine dinucleotide hydrogen. $n = 10$/group. $^{*}p < 0.05$, $^{***}p < 0.005$, two-way ANOVA (A-E) or student's t-test (**F**).

to anesthetics. NADH, a common NAD + precursor, may not improve or effect post-anesthetic locomotive or cognitive performance despite its promising use to prevent and treat dementia.

Our results need to be considered within the context of potential limitations. We demonstrated a decrease in activity after acute NADH administration in young and otherwise healthy mice. However, the primary patient population that is targeted for NAD supplementation are aged adults and those with neurodegenerative disease. The response in aged rodents may differ or may be even more pronounced than what we've observed in young mice which will require further study. In addition, NADH was acutely administered via intraperitoneal injection just prior to emergence and may not necessarily be representative of how chronic oral NAD supplementation may impact recovery from general anesthesia. This may explain why our study differs from the improvement in cognitive performance seen by others with chronic NAD administration in rodents[28]. Additionally, behavioral assessments of recovery in mice may not fully capture the complexity of cognitive and neurologic recovery in humans following anesthesia. While a decrease in locomotor activity was observed, the implications of this behavior in rodents remain unclear. The lack of molecular or cellular measures of brain function in our study limits our ability to interpret whether NADH exerts any effects on longer-term recovery or brain health. Importantly, no biochemical data were obtained to explore the underlying mechanisms driving these behavioral differences. Further studies are needed to examine potential changes in mitochondrial function, neuronal signaling, or other pathways that could validate the mechanistic basis for the observed effects. Lastly, the depressed open-field behavior after NADH was seen irrespective of anesthetic exposure. We can only conclude that NADH does not enhance recovery from anesthesia and cannot conclude that there is a negative effect on behavior after emergence from anesthesia since there is an effect at baseline. Regardless, acute administration of NADH altered rodent behavior which underscores that there are differences in the effect of acute and chronic administration of NAD. Further, although the mechanism through which NADH slows open-field activity is not known, this interesting observation that NADH decreases locomotor activity after anesthesia warrants further investigation.

This study explores the effects of NADH, a common over-the-counter NAD + precursor, on cognitive and locomotor recovery after anesthesia in rodents. Despite the interest in NAD + for its potential benefits in brain aging, our findings indicate that acute NADH administration decreases rodent activity and has no effect on spatial memory performance following general anesthesia. The mechanisms underlying these effects should be evaluated in future research, as well as the potential benefits or risks of discontinuing NAD supplements in the perioperative period.

Methods

Procedures and protocols were approved by the Animal Care and Use Committee at Stanford University under AAPLAC #31,510 (Stanford, CA, USA) and all methods were performed in accordance with their guidelines and regulations. In addition, the study was conducted in accordance with ARRIVE guidelines. Twelve- to sixteen-week old male and female (equal distribution) C57BL/6J mice (Jackson Labs, Sacramento, CA) were used. Based on an a priori power analysis (a = 0.05 and 80% power), we determined that $n = 8$ mice were needed for the open-field behavior studies, and $n = 10$ were needed for Y-maze behavioral studies.

The drugs used in the study included NADH (150 mg/kg[32], intraperitoneal, Thermo Fisher Scientific, Catalog No. AAJ6163803, Waltham, MA) diluted in 0.9% normal saline for an end concentration of 45 mg/ml and volume-matched vehicle (0.9% normal saline). The pH of the NADH solution was 5.71, near to that of commercially available 0.9% saline with a pH of 5.6. To determine how NADH impacted recovery from general anesthesia, a sub-set of rodents received isoflurane (1.5%, inhalational, VetOne, Boise, Idaho) prior to NADH or vehicle administration.

The first sub-set of mice received NAD without general anesthesia while a different sub-set of mice received NAD with general anesthesia (Fig. 1). For mice receiving NAD without general anesthesia, baseline and post-treatment open field activity was recorded (Fig. 1A). After 15 min acclimation, the baseline open field activity was recorded for 15 min in all mice. Mice were then given NADH or vehicle and returned to the open field to continue recording for 30 min post-treatment.

For mice receiving NADH with anesthesia, the baseline activity was recorded prior to anesthesia and the treatment was given prior to emergence from anesthesia (Fig. 1B). After 15 min acclimation, the baseline open field activity was recorded in all mice. Mice were then anesthetized in an induction chamber on a heating pad with 1.5% isoflurane for 30 min. Induction chambers were placed on heating pads set at 45 °C and all mice were maintained at the same temperature during the anesthetic. The heating pad was turned off after the mice regained their righting reflex. The respiratory rate and color of all mice were observed during the anesthetic to ensure there were no periods of hypoxia. The mice then received NADH or vehicle just prior to emergence and returned to the open field to continue recording for 30 min post treatment. In a separate cohort of mice, the Y-maze performance was assessed at baseline and post treatment.

The behavioral assays used to assess general locomotor activity and short-term memory included open field activity and Y-maze[33]. For open field activity, activity was recorded after the return of the righting reflex for a period of 30 min to assess recovery after anesthesia. Open-field activity was analyzed by a blinded observer using Biobserve (Bonn, Germany) tracking software. The percent time a mouse was active in an open-field (defined as movement with a minimum velocity of 0.5 cm/s) was recorded and normalized to the pre-treatment baseline activity. Y-maze activity was recorded 30 min after the emergence from anesthesia with NADH or vehicle. After recovery for 30 min after anesthesia, mice were placed in the Y-maze with 2 arms open (start and alternate arms) for a period of 10 min and returned to their cage for 30 min. Mice were then returned to the Y-maze with all 3 arms open, and activity was recorded for 10 min. The Y-maze activity was analyzed by a blinded observer using Biobserve Viewer 3 (Bonn, Germany, www.behavioralinstruments.com) tracking software.

GraphPad Prism version 10.3.1 (Boston, MA, www.graphpad.com) was used for statistical analysis. Data are expressed as mean ± SEM. An unpaired Student's t test was used to compare two groups while for multiple time points ANOVA with Bonferroni correction was used. Statistical significance was defined as $p < 0.05$.

Data availability

All data generated and analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

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Author contributions

C.G. designed and executed experiments and wrote main manuscript text J.M. executed experiments and wrote methods E.C. and E.F. executed experiments E.G. wrote and edited main manuscript text.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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