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TrkB receptor signaling in the nucleus tractus solitarius mediates the food intake-suppressive effects of hindbrain BDNF and leptin

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Spaeth AM, Kanoski SE, Hayes MR, Grill HJ. TrkB receptor signaling in the nucleus tractus solitarius mediates the food intake-suppressive effects of hindbrain BDNF and leptin. Am J Physiol Endocrinol Metab 302:E1252–E1260, 2012. First published February 28, 2012; doi:10.1152/ajpendo.00025.2012.—Brain-derived neurotrophic factor (BDNF) and TrkB receptor signaling contribute to the central nervous system (CNS) control of energy balance. The role of hindbrain BDNF/TrkB receptor signaling in energy balance regulation is examined here. Hindbrain ventricular BDNF suppressed body weight through reductions in overall food intake and meal size and by increasing core temperature. To localize the neurons mediating the energy balance effects of hindbrain ventricle-delivered BDNF, ventricle subthreshold doses were delivered directly to medial nucleus tractus solitarius (mNTS). mNTS BDNF administration reduced food intake significantly, and this effect was blocked by preadministration of a highly selective TrkB receptor antagonist ([N2–2-Oxazepan-3-yl amino]carbonyl phenyl benzo (b)thiophene-2-carboxamide (ANA-12)), suggesting that TrkB receptor activation mediates hindbrain BDNF’s effect on food intake. Because both BDNF and leptin interact with melanocortin signaling to reduce food intake, we also examined whether the intake inhibitory effects of hindbrain leptin involve hindbrain-specific BDNF/TrkB activation. BDNF protein content within the dorsal vagal complex of the hindbrain was increased significantly by hindbrain leptin delivery. To assess if BDNF/TrkB receptor signaling acts downstream of leptin signaling in the control of energy balance, leptin and ANA-12 were coadministered into the mNTS. Administration of the TrkB receptor antagonist attenuated the intake-suppressive effects of leptin, suggesting that mNTS TrkB receptor activation contributes to the mediation of the anorexigenic effects of hindbrain leptin. Collectively, these results indicate that TrkB-mediated signaling in the mNTS negatively regulates food intake and, in part, the intake inhibitory effects of leptin administered into the NTS.

Address for reprint requests and other correspondence: H. J. Grill, Dept. of Psychology, Univ. of Pennsylvania, 3720 Walnut St., Philadelphia, PA 19104 (e-mail: grill@psych.upenn.edu).
to food intake (55, 57), we examined whether 4th icv BDNF increased correlates of energy expenditure (core temperature and locomotor activity). To address whether NTS-specific TrkB signaling is responsible for mediating the intake-suppressive effects of hindbrain ventricular delivery of BDNF, ventricle subthreshold doses of BDNF were delivered to medial NTS (mNTS) parenchyma, and subsequent food intake and body weight gain were assessed. In addition, BDNF was coadministered to the NTS with a newly developed, highly selective TrkB receptor antagonist ([N2–2-2-Oxaoazepan-3-yl amino]carbonyl phenyl benzo (b)thiophene-2-carboxamide (ANA-12)) (7). This compound was also used to evaluate whether the anorexic effects of NTS leptin administration are mediated in part by the downstream effects of BDNF/TrkB signaling. Collectively, the results demonstrate that NTS-specific BDNF/TrkB receptor signaling is a contributor to the anorectic effects of NTS leptin receptor activation and that BDNF/TrkB receptor activation in the hindbrain regulates energy balance by suppressing food intake specifically through a reduction in meal size and by increasing core temperature.

METHODS

Subjects

Adult male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 275–350 g at the time of surgery were housed individually in hanging wire-bottom cages and maintained in a temperature-controlled room on a 12:12-h light-dark cycle. Separate cohorts of animals were used for each experiment. For food intake and meal pattern experiments, lights were off from 1000 to 2200, and for energy expenditure experiments, lights were off from 2100 to 0900. Water and either powdered or pelleted rodent chow (Purina 5001; Purina, St. Louis, MO) were available ad libitum unless otherwise noted. All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania.

Surgery

Each rat was anesthetized with an intramuscular injection containing ketamine (90.0 mg/kg), xylazine (2.7 mg/kg), and acepromazine (0.64 mg/kg) and given an analgesic Metacam (0.20 mg) via subcutaneous injection. Rats received a guide cannula (22-gauge; Plastics One, Roanoke, VA) with its tip positioned stereotaxically 2.0 mm above either the 4th ventricle (coordinates: on the midline, 2.5 mm anterior to the occipital suture and 5.2 mm ventral to the skull, with injector aimed 7.2 mm from skull) or the medial NTS at the level of the AP (coordinates: midline ± 0.75, 1.0 mm posterior to the occipital suture and 6.9 mm ventral to the skull, with injector aimed 8.9 mm from skull) (20, 21, 47, 48, 51). Cannula were attached to the skull with dental acrylic and jeweler’s screws and closed with obturators. In rats designated for recording core temperature and spontaneous activity, a small midline abdominal incision was made, and a telemetric transponder (G-2; MiniMitter, Bend, OR) was inserted into the abdominal cavity. Rats recovered for at least 1 wk prior to the start of testing. These transponders enable the recordings of average core temperature and spontaneous activity every 5 min, as described previously (49, 50). At least 5 days after surgery, injection placement was assessed by measurement of the sympathoadrenal-mediated hyperterglycemcemic response to the cytogluconeopnia-induced 5-thio-β-glucose (210 µg for the 4th ventricle and 24 µg for the NTS) dissolved in artificial cerebrospinal fluid (aCSF) (44). Only data from rats showing at least a twofold increase in plasma glucose level in response to this treatment were included in the analyses. mNTS injection placement was also verified postmortem through verification of the position of 100 nl of pontamine sky blue ink injections.

Drug Preparation and Injections

Human recombinant BDNF (Tocris, Ellisville, MO) was dissolved in aCSF, the specific TrkB receptor antagonist ANA-12 (Maybridge, Cornwall, UK) was dissolved in dimethyl sulfoxide (DMSO) (7), and leptin (National Hormone & Peptide Program) was dissolved in 0.01 M sodium bicarbonate. Drugs were stored at −80°C prior to use.

Automated Feeding Apparatus

In experiment 1, cumulative food intake was measured with a specialized automated feeding system (DiaLog Instrument, Tallahassee, FL). Briefly, rats were housed individually in cages equipped with an access port to a food cup seated on a load cell circuit that reported to an interface and a computer with customized software for data display, storage, and analysis (LabVIEW, National Instruments). The weight of the food cup was measured every 10 s, enabling assessment of meal parameters (see below for criteria) and cumulative intake for the 24-h recording period without the rats being disturbed.

Experimental Procedures

Experiment 1: effects of acute 4th icv BDNF on food intake and body weight. Rats (n = 11) received 4th icv injections of BDNF (0, 0.1, 0.2, 0.5, 1.0, or 2.0 µg) in a counterbalanced fashion immediately prior to the onset of the dark cycle. Doses of BDNF were selected from pilot work. After acute injections rats were given their food, and the automated feeding system was initiated. Meals were defined as an episode of feeding in which a minimum of 0.25 g was ingested, with meal termination criterion as the beginning of a pause in ingestion no less than 10 min in duration (1). This was determined using the cumulative data from the automated feeding apparatus and objectively calculated using a Microsoft Excel macro. Body weight measurements were made immediately before and 24 h after the injection of the drug.

Experiment 2: effects of 4th icv BDNF on correlates of energy expenditure. Approximately 1 h into the light cycle, food was removed and the Minimitter system engaged to record 1 h of baseline data. After this hour, each rat (n = 8) received counterbalanced 4th icv injections of BDNF (0 or 2.0 µg). The BDNF dose was chosen on the basis of the results of experiment 1, which showed that the 2-µg BDNF dose reduced food intake and body weight. After injections, food was removed from the cage and energy expenditure measured for 6.5 h, and food was then returned. The handling of the animal during injections produces a transient spike in core temperature and activity. Therefore, energy expenditure was quantified as the average core temperature and activity beginning 1.5 h after the injection (when activity levels stabilized) until the end of the 6.5-h recording period. As described previously, food was not available during the period of energetic response measurement to avoid diet-induced thermogenesis, which could have confounded the interpretation of the effects of BDNF on energy expenditure (47, 49). Food intake and body weight measurements were made immediately before and 24 h after the injection of the drug.

Experiment 3: effects of mNTS BDNF on food intake and body weight gain. Rats (n = 8) received counterbalanced unilateral NTS intraparenchymal injection of BDNF (0, 0.2, or 0.5 µg) immediately prior to the onset of the dark cycle. Doses of BDNF were selected from the results of experiment 1; two doses that were subthreshold for food intake and body weight suppression following 4th ventricle delivery were used. The doses used were consistent with the range of intraparenchymal doses applied to the hippocampus in work on the antidepressant action of BDNF (45). After the injections rats were given access to food, and intake was measured at 1, 3, and 6 h after the injection by an investigator. Body weight measurements were made immediately before and 24 h after the injection of the drug.

Experiment 4: BDNF/TrkB receptor signaling within the mNTS. All rats (n = 9) received two unilateral NTS intraparenchyma injections that were ~20 min apart, and food intake was determined at 1, 3, 6,
and 24 h after the second injection. Conditions were counterbalanced and were as follows: control condition (100 nl of DMSO followed by 100 nl of aCSF), ANA-12 condition (1 or 3 μg of ANA-12 followed by aCSF), BDNF condition (DMSO followed by 0.2 μg of BDNF), and the combination condition (either 1 or 3 μg of ANA-12 followed by 0.2 μg of BDNF). Body weight measurements were made immediately before and 24 h after the injection of the drugs.

Experiment 5: Effect of Hindbrain Leptin Administration on Hindbrain BDNF Levels. To examine the effects of hindbrain leptin receptor activation on DVC BDNF protein content, rats (n = 8; ad libitum maintained) received 4th icv injections (either sodium bicarbonate or 4.0 μg of leptin) 1 h into the light cycle. Two hours after the injection, rats were euthanized by decapitation. Brains were rapidly removed and tissue lysates collected from the DVC and flash-frozen in −70°C isopentane, as described previously (19, 22). Concentrations of BDNF protein content in the tissue lysates were assessed using a two-site enzyme immunoassay kit (Millipore, Billerica, MA), following the manufacturer’s instructions. BDNF concentrations were determined from the regression line for the standard (ranging from 7.8 to 500 pg/ml purified BDNF) incubated under similar conditions in each assay. The cross-reactivity with other related neurotrophins was <3%. All assays were performed in duplicate.

Experiment 6: Hindbrain TrkB Receptor Signaling and Leptin. All rats (n = 9) received two unilateral NTS parenchyma injections that were ~20 min apart, and food intake was measured at 1, 3, 6, and 24 h after the second injection. The four counterbalanced conditions were as follows: control condition (100 nl of DMSO followed by 100 nl of sodium bicarbonate), ANA-12 condition (3 μg of ANA-12 followed by sodium bicarbonate), leptin condition (DMSO followed by 0.2 μg of leptin), and the combination condition (3 μg of ANA-12 followed by 0.2 μg of leptin). Body weight measurements were made immediately before and 24 h after the injection of drugs.

Statistical Analysis

Data (means ± SE) for all experiments were assessed using one- or two-way repeated-measures analysis of variance (ANOVA) with drug treatments as the independent variable. Analyses were made using Statistica software (version 7.0, StatSoft, Tulsa, OK), with P < 0.05 considered statistically significant. Planned comparisons to vehicle were used for dose-response studies. Newman-Keuls post hoc comparisons were used for significant drug interactions.

RESULTS

Experiment 1: Effects of Acute 4th icv BDNF on Food Intake and Body Weight

Hindbrain delivery of BDNF (4th ventricle) suppressed cumulative food intake and body weight (Fig. 1, A and B) in a dose-dependent manner. ANOVA revealed a significant main effect of BDNF dose on 6-h food intake [F(5,35) = 6.20, P < 0.001], 24-h food intake [F(5,35) = 6.66, P < 0.001], and body weight [F(5,35) = 2.88, P < 0.05]. Individual dose comparisons with vehicle treatment showed that the two highest doses, 1.0 and 2.0 μg, suppressed food intake significantly at both 6 (P < 0.05) and 24 h (P < 0.05). The 1.0-μg BDNF dose suppressed body weight significantly relative to vehicle (P < 0.05); the 2.0-μg dose also suppressed body weight, but the effect was a trend that almost reached significance (P = 0.08).

Meal pattern analysis of the food intake effects of hindbrain BDNF revealed that the suppression of cumulative intake at 6 and 24 h by the 1.0- and the 2.0-μg doses is explained by an
effect on meal size and not by meal number (Fig. 1, C and D). Hindbrain BDNF-treated rats consumed smaller meals during the dark cycle compared with vehicle treatment \( F(5,35) = 2.58, P < 0.05; \) Fig. 1C. Figure 1C also shows that hindbrain BDNF delivery of two lower doses of BDNF (0.2 and 0.5 µg) also reduced meal size \( (P < 0.05). \) For these doses, unlike for 1.0- and 2.0-µg doses, a significant increase in meal frequency compensated for the effect of reduced meal size on cumulative intake \( (P < 0.05; \) Fig. 1D).

**Experiment 2: Effects of 4th icv BDNF on Correlates of Energy Expenditure**

Hindbrain BDNF delivery of a dose (2.0 µg) that was shown to suppress feeding in experiment 1 increased core temperature significantly when examined in the home cage during the light phase and in the absence of food \( F(1,7) = 3.055, P < 0.05; \) see Fig. 2B. This treatment was without effect on spontaneous activity relative to vehicle treatment \( (F = 1.0); \) data not shown.

**Experiment 3: Effects of mNTS BDNF on Food Intake and Body Weight Gain**

Direct mNTS parenchymal delivery of two doses of BDNF that were shown to be ineffective when delivered to the 4th ventricle (Fig. 1, A and B) significantly and potently suppressed food intake 24 h after drug administration \( F(2,14) = 15.69, P < 0.01; \) a similar effect was observed 6 h after drug administration \( F(2,14) = 4.22, P = 0.08; \) Fig. 3A]. Dose comparisons with vehicle showed that both 0.2- and 0.5-µg doses of BDNF suppressed feeding significantly at 24 h \( (P < 0.05). \) Body weight was reduced significantly 24 h after mNTS BDNF administration \( F(2,14) = 8.97, P < 0.05, \) significant for the 0.2- and the 0.5-µg doses, \( P < 0.05; \) Fig. 3B].

**Experiment 4: BDNF/TrkB Receptor Signaling Within the mNTS**

To evaluate NTS TrkB mediation of the food intake inhibitory effect of mNTS parenchymal BDNF delivery, two doses of a recently described TrkB antagonist were evaluated with separate analyses run for each dose of the TrkB antagonist. For the 1-µg ANA-12 dose analysis, a significant main effect of BDNF \( [F(1, 8) = 8.56, P < 0.05; \) Fig. 4A] and ANA-12 \( [F(1, 8) = 9.01, P < 0.05] \) was obtained for 24-h food intake, and a significant main effect of BDNF \( [F(1, 8) = 7.14, P < 0.05; \) Fig. 4B] was found for 24-h body weight change. Post hoc analyses revealed that BDNF administration reduced 24-h food intake significantly when administered alone to the mNTS \( (P < 0.05) \) but that preadministration of ANA-12 blocked this potent intake-suppressive effect; the combination condition was significantly different from the BDNF condition alone \( (P < 0.05). \)

For the 3-µg ANA-12 dose analysis, repeated-measures ANOVA revealed a significant BDNF × ANA-12 interaction \( [F(1, 8) = 6.94, P < 0.05; \) Fig. 4A] for 24-h food intake and a main effect of BDNF \( [F(1, 8) = 7.14, P < 0.05; \) Fig. 4B] for 24-h body weight change. Post hoc analyses revealed that BDNF administration reduced 24-h food intake and body weight significantly when administered alone to the mNTS \( (P < 0.05) \) but that preadministration of ANA-12 blocked
these potent intake and body weight-suppressive effects. For 24-h food intake and body weight change, the combination condition was significantly different from the BDNF condition alone ($P < 0.05$).

**Experiment 5: Effect of Hindbrain Leptin Administration on Hindbrain BDNF Levels**

Figure 5 shows that hindbrain leptin delivery (4th icv) 120 min prior to euthanization increased BDNF protein content within DVC tissue significantly [$F(1,6) = 9.41, P < 0.05$], as measured by ELISA.

**Experiment 6: Hindbrain TrkB Receptor Signaling and Leptin**

TrkB receptor antagonism attenuated the anorexigenic effects of mNTS leptin administration 6 h after drug administration. There was a significant ANA-12 × leptin interaction [$F(1,8) = 10.90, P < 0.05$; Fig. 6] for 6-h food intake. Post hoc analyses revealed that leptin reduced 6-h food intake significantly when administered alone to the mNTS ($P < 0.05$) but that preadministration of ANA-12 blocked these intake-suppressive effects; the combination condition differed significantly from the leptin alone condition ($P < 0.05$). Leptin also decreased intake at 24 h; however, this main effect did not reach significance ($P = 0.08$), and there were no effects of ANA-12 (Fig. 6). There were no significant differences between conditions on change in body weight 24 h after drug administration ($F < 1$; data not shown).

**DISCUSSION**

A range of data, including genetic studies in humans and rodent models as well as pharmacological and biochemical experiments in rodents, provide direct evidence for an important role of BDNF in energy homeostasis (15, 18, 36). Although the neuroanatomic basis for the effect of BDNF on food intake and body weight involves hypothalamic BDNF/TrkB signaling (54 –57), recent findings suggest that DVC BDNF/TrkB signaling also contributes to the food intake effects of...
BDNF (2, 3). The multisite nature of BDNF’s energy balance effects is consistent with the view that the contribution of BDNF/TrkB signaling is more likely to be neuroanatomically distributed than it is to be localized to one brain region (17). Results from the experiments reported here provide support for this distributed control perspective by showing that 1) hindbrain-delivered BDNF increases core temperature, 2) the hindbrain BDNF dose-related reductions in feeding result from reductions in the size of meals and not meal number, 3) mNTS neurons are direct targets of BDNF’s effect on food intake since doses that were ineffective when delivered to the 4th ventricle in experiment 1 were shown to potently reduce food intake and body weight when delivered to mNTS parenchyma, and 4) the food intake inhibitory effects of NTS BDNF delivery were mediated by an action on local TrkB receptors. Given that leptin inhibits feeding in part by activating melanocortin neurons and that the inhibition of feeding by melanocortin neurons involves downstream BDNF pathways (3, 8, 59), the current experiments also investigated whether the intake inhibitory effects of mNTS leptin administration were mediated in part by downstream BDNF/TrkB receptor signaling. We showed that hindbrain leptin delivery increased the expression of BDNF protein in DVC tissue and that the intake inhibitory effects of mNTS leptin administration were mediated in part by downstream BDNF/TrkB receptor signaling.

Exogenous BDNF delivery to a forebrain ventricle or directly to the VMN and PVN triggered energetic effects (37, 55, 57). Prior to the current study there were no investigations into the energetic effects of hindbrain-targeted BDNF delivery. Here, we show that hindbrain ventricular BDNF delivery elevated core temperature (a correlate of energy expenditure) without affecting locomotor activity during the light cycle. Future studies should examine further the effect of hindbrain BDNF administration on locomotor activity during the dark cycle, when animals are more active. Given the caudal flow of the cerebral spinal fluid, these hindbrain ventricular effects are mediated by local action and not by rostral diffusion of drugs (11). Identifying specific hindbrain neurons that mediate BDNF’s thermogenic effect requires further study. Candidates include neurons of the AP, NTS, caudal raphe, and giganto-cellular reticular nucleus, all of which are known to contribute to the mediation of thermogenic responses (34) and to also contain TrkB receptors (10, 25, 29).

One aim of this study was to explore the hypothesis that hindbrain BDNF/TrkB signaling contributes to the mediation of the anorexic effects of hindbrain leptin signaling. Support for this hypothesis is provided by several of the current findings. First, the observed core temperature elevation without increased activity observed with hindbrain BDNF administration is the same pattern of effect reported for hindbrain ventricular leptin delivery (50). Second, hindbrain leptin administration significantly increased BDNF protein content in the DVC, a finding that complements those of Bariohay et al. (2), who reported increases in DVC BDNF protein content after systemic leptin treatment, and those of Moyse et al. (32), who reported increases in DVC BDNF in aged rodents with hyperleptinemia. Finally, by examining the food intake effect of NTS parenchymal leptin delivery, NTS delivery of the TrkB-selective antagonist (ANA-12), and their combination, we show a significant attenuation of the NTS leptin-induced anorexia when coadministered with a dose of ANA-12 that had no feeding effect of its own.

The nature of the mechanism by which leptin receptor activation in the NTS leads to an increase in BDNF signaling...
has not been established. Hindbrain BDNF/TrkB receptor signaling may contribute to the control of food intake and energy expenditure by modulating neurotransmission, regulating neuronal growth and synapse formation, altering synaptic plasticity of NTS neurons, and/or engaging common intracellular signaling pathways implicated in energy balance regulation. BDNF vesicle clusters are found close to active synapses (pre- and postsynaptically), and their content is released in response to synaptic stimulation (6). Once activated, the TrkB receptor engages a number of intracellular signaling responses, including activation of the MAP kinase and phosphoinositide 3-kinase pathways (38, 45), both of which are also implicated in energy balance control following activation of leptin receptors (35, 41). It is possible that intracellular signaling pathways downstream of leptin receptor activation directly trigger BDNF release, which in turn modulates the synaptic transmissions from these NTS neurons to other CNS nuclei implicated in energy balance regulation. One particular leptin intracellular signaling pathway of interest is the activation of the Ras-Ref mitogen-activated protein kinase kinase (MEK), which promotes extracellular signal-regulated kinase 1/2 activity and the phosphorylation of the transcription factor cAMP response element-binding protein (CREB). Weng et al. (58) recently showed that leptin administration in the substantia nigra of mice led to a marked increase in the levels of BDNF and that this effect was blocked when CREB and MEK were inhibited.

Diet and energy status modulate CNS BDNF levels and BDNF-mediated neuronal plasticity and neurogenesis within the hippocampus (12, 23, 27, 28, 30, 39). Whether neuronal plasticity is altered in the hindbrain in response to BDNF levels has not been examined. Interestingly, we did not observe food intake suppression by hindbrain BDNF until 6 h after injection, an effect that persisted until 24 h after injection. These relative long-latency and prolonged effects of BDNF on feeding leave open the possibility that BDNF may reduce food intake by modulating neurotransmitter release and subsequent synaptic formation and plasticity (6). It was shown recently that leptin can induce rapid rewiring of synaptic inputs to key neurons in the hypothalamus (neuropeptide Y and proopiomelanocortin cells), which likely accounts for some of the ligand’s behavioral effects on food intake and body weight (40). Furthermore, BDNF acts at postsynaptic sites to modulate excitatory transmission at glutamatergic primary afferent synapses in the NTS (9). Whether alterations in glutamatergic signaling mediate BDNF’s anorectic effects in the mNTS and its potential effects on synaptic connectivity in the mNTS requires further study. It has also been shown that leptin has neurotrophic properties that lessen neuronal damage in experimental models of human neurological disorders (31, 46, 58). Therefore, it is reasonable that BDNF acts downstream of leptin signaling to mediate synaptic rewiring and changes in connectivity with other nuclei downstream of its own action to have energy balance effects.

In conclusion, the data presented reveal that hindbrain BDNF/TrkB signaling promotes negative energy balance by reducing meal size and increasing core temperature. Results show that mNTS TrkB receptors mediate the intake inhibitory effects of NTS BDNF delivery and demonstrate that TrkB-mediated signaling in the mNTS negatively regulates food intake. NTS leptin receptor signaling is mediated in part by NTS BDNF/TrkB signaling, since hindbrain leptin increased BDNF protein content in DVC tissue, and food intake suppression by NTS leptin administration was attenuated by blockade of NTS TrkB receptors. Current findings also provide support for the hypothesis that NTS BDNF/TrkB receptor signaling occurs downstream of leptin activation and contributes to leptin’s effects on energy balance. The intake inhibitory effects mediated by NTS leptin receptor activation may possibly involve altered synaptic plasticity via the neurotrophic effects of BDNF on NTS neurons, which could subsequently increase the responsiveness of these neurons to other anorectic satiation signals.

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DISCLOSURES

The authors declare no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS

A.M.S., S.E.K., M.R.H., and H.J.G. approved the final version of the manuscript. A.M.S., A.M.S., and S.E.K. performed the experiments; A.M.S. and S.E.K. analyzed the data; A.M.S., S.E.K., M.R.H., and H.J.G. interpreted the results of the experiments; A.M.S. drafted the manuscript; A.M.S., S.E.K., M.R.H., and H.J.G. edited and revised the manuscript; A.M.S., S.E.K., M.R.H., and H.J.G. did the conception and design of the research; A.M.S. performed the experiments; A.M.S. and S.E.K. analyzed the data; A.M.S., S.E.K., M.R.H., and H.J.G. interpreted the results of the experiments; A.M.S. prepared the figures; A.M.S. drafted the manuscript; A.M.S., S.E.K., M.R.H., and H.J.G. edited and revised the manuscript; A.M.S., S.E.K., M.R.H., and H.J.G. approved the final version of the manuscript.

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