H_2S Induces a Suspended Animation–Like State in Mice

Eric Blackstone,[1,2] Mike Morrison,[2] Mark B. Roth[2]*

Many organisms respond to changes in environmental conditions by entering into a suspended animation–like state in which a decrease in metabolic rate (MR) is followed by a reduction in core body temperature (CBT) (*1*). Regulated induction of a hypometabolic state is hypothesized to have great medical benefit for a variety of conditions, including ischemia and reperfusion injury, pyrexia, and other trauma (*2*). Suspended animation–like states may also be useful for creating beneficial hypothermia in surgical situations and for improving organ preservation (*1*).

Inhibiting oxidative phosphorylation reversibly induces states of profound hypometabolism in several model organisms (*3*–*5*). Because hydrogen sulfide (H_2S) is a specific, potent, and reversible inhibitor of complex IV (cytochrome c oxidase), the terminal enzyme complex in the electron transport chain (*6*), we hypothesized that it could reduce MR and CBT in mammals.

When mice were exposed to 80 ppm of H_2S, their oxygen (O_2) consumption dropped by ~50% and their carbon dioxide (CO_2) output dropped by ~60% within the first 5 minutes (Fig. 1A) (*7*). If left in this environment for 6 hours, their MR dropped by ~90% (Fig. 1A). The MR of control mice, as judged from O_2 consumption and CO_2 output increases (*8*). This drop in MR was followed by a drop in CBT to ~2°C above ambient temperature (Fig. 1B). The average CBT of these mice reached a minimum of 15°C in an ambient temperature of 13°C (Fig. 1B). At this minimum CBT, both CO_2 output and O_2 consumption was ~10% of normal (Fig. 1A), and the breathing rate of the mice decreased from ~120 breaths per minute (BPM) to less than 10 BPM (*8*). After 6 hours of exposure to H_2S, the mice were returned to room air and temperature, and their MR and CBT returned to normal (Fig. 1, A and B).

Exposing mice to varying concentrations of H_2S revealed a linear relationship between the concentration of H_2S and CBT (Fig. 1C). CBT dropped faster and reached lower temperatures as concentrations of H_2S increased from 0 to 80 ppm (*8*), suggesting that the effects of H_2S are concentration-dependent. However, this MR reduction is not dependent on ambient temperature (fig. S1).

Because H_2S can be toxic in high doses, we conducted behavioral and functional tests, selected from the SHIRPA protocol (*9*), to assay for H_2S-induced damage. No behavioral or functional differences in the mice were detected after exposure to 80 ppm of H_2S for 6 hours (*8*). In the absence of H_2S, no effect on CBT was observed (Fig. 1B, control atmosphere). In addition, others report no long-term health effects with these H_2S concentrations (*6*).

The sequential drop in MR and CBT observed in mice (Fig. 1D) exposed to 80 ppm of H_2S is similar to that observed when animals initiate hibernation, daily torpor, or estivation (*1*). On-demand induction of a suspended animation–like state could provide insight into the mechanisms that govern natural states of reduced metabolism. Lowering metabolic demand in this way could be used to reduce physiological damage resulting from trauma and might improve outcomes after surgery.

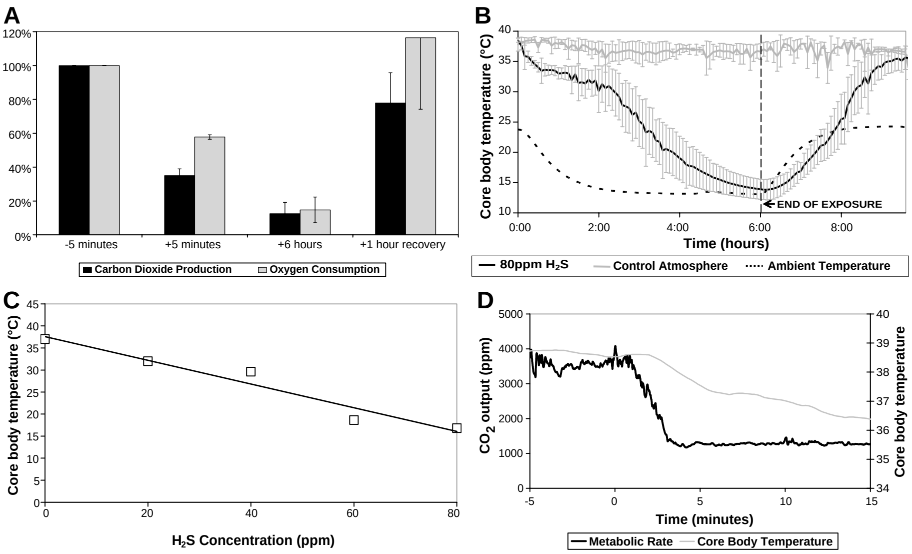

Fig. 1. CBT and MR of mice exposed to H_2S. (**A**) Relative CO_2 production and O_2 consumption of mice exposed to 80 ppm of H_2S. (**B**) CBT of mice during 6 hours of exposure to either 80 ppm of H_2S (black line) or the control atmosphere (gray line). The dotted line indicates ambient temperature. Values in (A) and (B) are means ± one standard deviation. (**C**) Linear relationship between H_2S concentration and CBT (R^2 = 0.95) after 6 hours of exposure. (**D**) CO_2 output and CBT of mice (time = 0 at the start of H_2S exposure).

References and Notes

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Fig. S1

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[1]Molecular and Cellular Biology Program, University of Washington, Seattle, WA 98195, USA. [2]Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98105, USA.

*To whom correspondence should be addressed. E-mail: mroth@fhcrc.org