added to a standard murine powdered chow available *ad libitum*, the BT reduction was significantly counteracted in a dose-dependent manner (0.063, 0.25 and 1.0 g/kg/day were tested) such that there was no significant difference for any dose on any treatment day from the normal mice (the *Acn* 1.0 g dose actually showed significantly higher BT than normal controls on days 5, 7 and 9 after cold initiation). BW gain tended to be lower in the *Acn*-treated mice compared with room temperature controls, but there was no difference between cold-stressed controls and *Acn*-treated mice. Since the *Acn* treatment did not increase core BT in mice under normal room temperature conditions, the authors concluded that *Acn* did not directly stimulate thermogenesis, but rather facilitated a non-shivering physiological thermoregulation that occurs in brown adipose tissue, wherein the heat is produced through the metabolism of free fatty acids in the mitochondria.

Of note, the procedures in the two studies mentioned above appear to have been undertaken only once daily at a time(s) which may have been convenient to the researchers. In the study by Wada *et al*.,[48] there is no mention of the LD schedule for the mice or the time of day of *Acn* dosing and RT measurements. Assuming that the mice were kept in dark at night and with lights on during the day, the study was most likely carried out in the morning (e.g., between 08:00 and 12:00 hours or 02–06 HALO). In the study by Makino *et al*.,[49] they reported that the mice were housed under a 12-hour L–12 hour D schedule with L-on from 07:00 to 19:00 hours and BT was measured between 13:00 and 15:00 hours, which would be in the middle of the daily resting span (06–09 HALO). Both of these studies were thus carried out at only one of the six different circadian times that we used in our study in order to consider the well-known circadian variation in mouse body temperature (i.e., BT reaches its minima during mid-L and maxima during mid-D). Thus, for proper comparison to the human sleep–wake schedule, an extrapolation of the 22-day study mouse protocol of Wada and the 10-day study protocol of Makino would require similar treatment(s) during rest/sleep (i.e., at night after sleep onset).

## CONCLUSION

*Acn* administered in two different doses (6C and 30C) to healthy mice at six times 4 hours apart over 24 hours each induced hyperthermia overall and in a significant time-dependent (i.e., circadian) manner, with greater effects during the resting (L) span in nocturnally active mice. These results suggest that time of day may significantly impact the outcome of not only *Acn,* but also other homeopathic treatments used in the field of pharmacognosy. A chronobiologic approach that considers timing presents a new perspective for exploring the temporal mechanisms of action(s) by *Acn* and other homeopathic compounds in relation to mitochondrial and genetic involvement in thermal regulation at the level of hypothalamic centers, as well as their affect on neuroendocrine–immune network interactions.[50] With regard to homeopathic treatments, the concept of "chronotherapy" should be considered in determining optimal dosing and time of treatment(s) in order to increase the desired outcome and decrease the undesired effects of homeopathic procedures. At the very least, time(s) of treatment(s) should be recorded and reported for any future comparisons.

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