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Temperature in the spotlight of drug abuse research

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This editorial summarizes *Temperature*'s special issue entitled "Temperature and Toxicology with a Focus on Drugs of Abuse" (2014, volume 1, issue 3), dedicated to the multiple recent discoveries related to the thermoregulatory effects of xenobiotics. Several basic and clinical studies on xenobiotic-induced hyperthermia are reported that propose novel mechanisms and treatments.

The United Nations 2014 World Drug Report[1] estimated that, in 2011, between 162 million and 324 million people (3.5–7.0% of the world's adult population) had used an illicit drug – mainly a substance belonging to the cannabis, opioid, cocaine, or amphetamine-type stimulants group – at least once. Drug abuse and drug dependence convey serious health risks at the individual level, and such overwhelming numbers represent a heavy burden to society as a whole, creating social and economic problems and contributing to crime. The management of risks associated with drug abuse requires a comprehensive multidisciplinary approach, for which a breadth of knowledge on the physiological effects of psychotropic drugs is certainly important. The recent special issue of *Temperature*, highlighted in this editorial, contributes to such knowledge and places body temperature in the spotlight of drug abuse research.

As summarized by Kiyatkin,[2] hyperthermia is a known effect induced by psychomotor stimulants, and pathological hyperthermia is a prominent symptom of acute intoxication with these drugs in humans. However, the modulation of body temperature by psychomotor stimulants may also be achieved without clear signs of intoxication. In fact, the study by Parrott and Young[3] (further discussed by Kiyatkin and Ren[4]), which was performed on dance-clubbers using 3,4-methylenedioxymethamphetamine (MDMA), indicates that the increase in body temperature in humans is not an unusual or extreme effect. The authors think that this hyperthermia is a typical consequence of MDMA consumption during dance-clubbing, where high levels of psychophysiological and motor activation occur in the hot and humid environment typical of rave-parties in night clubs. Kiyatkin and Ren[4] also explore the increased ratings of "thirst" and intense water consumption observed in MDMA users. The authors propose that hyperhydration poses a serious risk of developing potentially lethal vasogenic edema, as MDMA causes water retention in both the brain and body. Another study, reported in the same special issue by Zaretsky et al.,[5] suggests that the ergogenic effect of amphetamines in rats masks fatigue, but that this effect may be offset in a warm environment as the dose of amphetamine increases. This phenomenon certainly deserves further attention and additional studies in humans.

The portion of the special issue dedicated to the hyperthermic effects of psychotropic drugs is crowned by 3 reviews. The first one, by Kiyatkin,[2] examines the recent work of his group on the increases in brain temperature caused by several well-known and recently introduced psychostimulant drugs of abuse: cocaine, methamphetamine, MDMA, methylone and 3,4-methylenedioxypyrovalerone. The author pays special attention to the role of activity state and environmental conditions in modulating the effects of these drugs on brain temperature and their acute toxicities. A chief assumption of this review is that the pathological brain hyperthermia induced by the overdose of psychomotor stimulants under rave conditions results from not only excessive heat production (due to the direct effects of drugs on tissue metabolism and indirect effects via psychophysiological activation), but also limited heat loss (due to the powerful drug-induced peripheral vasoconstriction in concert with the high ambient temperature and humidity of the clubbing environment). The second review, by Liechti,[6] focuses on the clinical studies of MDMA-induced hyperthermia and provides data about its mechanisms (the underlying sympathomimetic toxicity) and management. The authors of the third review, Dao et al.,[7] present a survey of pharmacologic agents that can lead to hyperthermia. They also review both established and candidate molecular mechanisms that regulate thermogenesis in heat-production effectors (brown adipose tissue and skeletal muscle). The authors identify carvedilol, a drug that

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Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine, ROS, reactive oxygen species.

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is usually used to treat congestive heart failure, as a potential new treatment of toxic hyperthermia.

From the data available so far, it has become clear that the multiplicity and complexity of thermoregulatory phenomena requires a unified theoretical framework accounting for an extensive set of known experimental facts. As a step in this direction, Molkov and Zaretsky[8] extend their recent publication[9] and present a mathematical model aimed at identifying the essential mechanisms of methamphetamine-evoked body temperature fluctuations. This model involves the balance of excitatory and inhibitory pathways activated by this drug. The authors hope their model can aid in assessing the activity of functional neuronal populations in freely-moving animals while using body temperature as an easy-to-measure physiological endpoint.

It is an indisputable fact that hyperthermia potentiates the neurotoxic effects of amphetamines, and this subject is addressed in the review by Bowyer and Hanig.[10] Their review highlights multiple events occurring at the whole body, tissue and molecular levels. At the tissue and body levels, the authors analyze the breakdown in the blood-brain barrier, the generation of seizures, and muscle and liver damage and discuss their pathophysiological significance. At the molecular level, the authors highlight the roles of protein misfolding, changes in neuronal ion channel permeability and the generation of reactive oxygen species (ROS). ROS are also in the center of the original study published in the same issue by Sanchez-Alavez et al.[11] The authors show that the ROS scavenger N-acetyl cysteine, when administered prior to or during the onset of methamphetamine-induced hyperthermia, ameliorates the body temperature increase and preserves mitochondrial integrity. While heat produced by motor activity contributes to methamphetamine-induced hyperthermia, N-acetyl cysteine does not eliminate motor agitation. The authors think that ROS scavengers can dissociate the hyperthermic and hyperkinetic effects and may be of potential utility in treating the hyperthermia associated with methamphetamine abuse.

Body temperature is also affected by other ordinary psychotropic substances, like alcohol and tobacco. In the same issue, Høiland et al.[12] report the effect of oral uptake of nicotine in snus (a moist powder tobacco product popular in Scandinavia) on peripheral skin blood circulation evaluated by thermography. This is the first report showing that the oral use of smokeless tobacco in snus decreases peripheral cutaneous circulation. This information may be important for patients with comprised peripheral blood flow and in situations where healthy users of tobacco snus are exposed to cold.

Hypothermia, as a defense mechanism, is also addressed in the special issue discussed in this editorial. In this issue, Nalivaiko et al.[13] present a review on motion sickness, nausea and thermoregulation. The authors provide evidence that the physiological mechanisms of motion sickness-associated hypothermia include both increased heat loss (cutaneous vasodilation and sweating) and reduced heat production (thermogenesis). They suggest that nausea, a natural defense against poisoning, is coupled with active hypothermia – another evolutionarily developed defense response.

Finally, a series of reports by Ramsay, Woods and Kaiyala,[14-16] further discussed by Flouris,[17] provides fresh and stimulating views on the way endothermic thermoregulation works. From the toxicology point of view, the authors' findings advance our understanding of addiction. Their recent investigations into the behavioral and autonomic effector responses elicited by chronic exposure to nitrous oxide indicate that highly responsive individuals (those who rapidly mount a compensatory response to the drug's pharmacological effect) appear relatively insensitive at the level of a feedback-controlled output (e.g., core temperature). These individuals are poised to readily acquire chronic tolerance and subsequently develop "hypertolerance." The authors view these findings as departing from the canonical homeostatic framework and being more compatible with an allostatic interpretation. The authors thoroughly analyze the concept of allostasis in their recent review[18] and a related piece[19] in the special issue under discussion.

In summary, the discussed special issue of *Temperature* reports on multiple recent discoveries in the biomedical sciences dealing with thermoregulatory effects of xenobiotics, with special emphasis on drug abuse. It was not our aim to comprehensively cover each study published in this special issue. Rather, we wanted to unveil some of the most relevant, interesting and important phenomena and conclusions, thus stimulating curiosity in our readers. As stated in *Temperature*'s inaugural editorial,[20] the journal aims at becoming a thermoregulation club, a discussion forum, an intellectual magnet, a feedback provider, a science news room . . . . Readers' curiosity is exactly what *Temperature* strives to both satisfy and encourage.

Disclosure of Potential Conflicts of Interest

FC, EAK and DER served as Guest Editors for the discussed special issue. AAR serves as *Temperature* Editor-in-Chief.

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