Carvedilol inhibits the cardiostimulant and thermogenic effects of MDMA in humans: Lost in translation

We greatly appreciate the comments offered by Drs Rolle, Takematsu, and Hoffman and the opportunity to put our work into a wider perspective. We share the view that our work does not reflect the clinical situation but rather provides a proof of mechanism study, which aims to help to translate preclinical findings (Sprague et al., 2005) into the clinic.

As we noted in the discussion of our work (Hysek et al., 2012b) the primary goal of the study was to investigate the role of adrenoceptors in the mechanism of action of MDMA in humans. Therefore, the study provided only indirect support for the use of carvedilol in the treatment of stimulant toxicity in which carvedilol would be administered following the ingestion of Ecstasy or other stimulants. Furthermore, we noted the limitation that the MDMA-induced increase in body temperature in our study was moderate and we do not know whether carvedilol would also be effective in cases of severe hyperthermia following ecstasy use.

The dose MDMA of 125 mg used in our controlled experimental study represents a commonly used recreational dose of MDMA. Rolle et al. cited findings from a naturalistic observational study in experienced ecstasy users in a party setting in Australia (Morefield et al., 2011). Of 49 partying subjects, 34 subjects used doses of MDMA of 0-150 mg and 15 users took cumulative doses of 150-280 mg (Morefield et al., 2011). The maximal total dose of MDMA was 280 mg. Most pills contained less than 100 mg of MDMA. A much larger study in 5,786 recreational drug users who handed in their tablets for analysis found that the average MDMA content in the ecstasy pills was 82.5 ± 35.2 mg (Brunt et al., 2012). Subjects presenting to emergency departments with any type of medical problems related to ecstasy use ingested less than two pills in 80% of the cases (Liechti et al., 2005; Williams et al., 1998). Importantly, desirable effects of MDMA were reported to show an inverse U-shaped dose-effect curve with doses of 60-140 mg of MDMA producing maximal desirable effects.
(Brunt et al., 2012). In contrast, doses larger than 140 mg produced less desirable and more adverse effects (Brunt et al., 2012). Thus, users have an interest in taking total doses in the range of 60-140 mg. Clinical trials in patients with posttraumatic stress disorder used doses of MDMA of 125 mg supplemented by 62.5 mg (Mithoefer et al., 2010; Oehen et al., 2013).

Severe hyperthermia is rare but it represents the most important complication of recreational MDMA use because of high mortality (Docherty et al., 2010; Henry et al., 1992; Parrott, 2012; Liechti et al., 2005; Rogers et al., 2009). The risk for MDMA-induced hyperthermic complications increases with repeated or high doses of MDMA (Parrott, 2012; Schutte et al., 2013), high ambient temperature (Dafters, 1995; Docherty et al., 2010), crowded conditions, physical exertion (Dafters, 1995), reduced fluid intake (Dafters, 1995), and hyperthyroidism (Martin et al., 2007; Sprague et al., 2007). One or several of these permissive factors are typically present in animal studies of MDMA-induced hyperthermia (Dafters, 1995; Schutte et al., 2013) and these risk factors should also be a concern in some recreational settings where MDMA and other amphetamines are consumed. For safety reasons these conditions are all avoided in controlled clinical studies. In controlled settings, MDMA produces only a small but well-documented increase in body temperature even in the absence of any known permissive factors (Hysek et al., 2012a; Hysek et al., 2012c; Liechti et al., 2001; Parrott, 2012).

Treatment of hyperthermia should primarily include hydration, sedation with benzodiazepines, and cooling. Dantrolene has been used in patients with extreme hyperthermia (Grunau et al., 2010). However, the use of dantrolene in sympathomimetic drug-induced hyperthermia is controversial (Rusyniak et al., 2004). MDMA-induced hyperthermia is not associated with a genetic disposition for malignant hyperthermia (Schutte et al., 2013) and it should not be misclassified as malignant hyperthermia. Other less promising candidate treatments of ecstasy-intoxicated patients have been discussed (Rietjens et al., 2012).
The mechanism of MDMA-induced thermogenesis involves serotonin (Docherty et al., 2010) as well as noradrenaline, $\alpha_1$ and $\beta_3$ adrenoceptors, and mitochondrial uncoupling proteins (Mills et al., 2003; Sprague et al., 2005; Sprague et al., 2007). Carvedilol blocked the effects of noradrenaline and not only significantly decreased the thermogenic effects of MDMA in humans but also reversed established MDMA-induced hyperthermia in rats when carvedilol was administered after MDMA (Sprague et al., 2005). Importantly, $\alpha$-$\beta$-blockers also effectively reduce the cardiostimulant effects of psychostimulants. It is critical to block both $\alpha$ and $\beta$ adrenoceptors to reduce increases in both blood pressure and heart rate (Boehrer et al., 1993; Hysek et al., 2012b). Blocking only $\alpha_1$ adrenoceptors lowered blood pressure and body temperature but enhanced heart rate increases in response to MDMA (Hysek et al., 2013). In contrast, blocking only $\beta$ adrenoceptors lowered tachycardia but enhanced the pressure response to cocaine (Ramoska et al., 1985) or MDMA (Hysek et al., 2010).

We agree with Rolle and colleagues that the true utility of carvedilol in the treatment of significant MDMA toxicity is unknown. We would therefore suggest that the benefit of carvedilol or other $\alpha$-$\beta$-blockers such as labetalol in patients presenting with drug-induced hyperthermia should further be evaluated. Because hyperthermic complications associated with psychostimulants are rare events, this can most likely only be done in single cases or case series and in the emergency medicine and critical care setting.

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References


Docherty JR, Green AR (2010). The role of monoamines in the changes in body temperature induced by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its derivatives. Br J Pharmacol 160: 1029-1044.


