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, α_1 and β_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, α-β-blockers also effectively reduce the cardiostimulant effects of psychostimulants. It is critical to block both α and β adrenoceptors to reduce increases in both blood pressure and heart rate (Boehrer *et al.*, 1993; Hysek *et al.*, 2012b). Blocking only α_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 β 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 α-β-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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