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Oral melatonin as a reducer of the neurotoxic and behavioral aftereffects of MDMA-usage

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Abstract

Ecstasy (XTC) is an amphetamine classed drug which is used worldwide, especially in the party-scene. The drug tends to give its users a warm, tendering, pro-social feeling and an increase in sensibility to lighting and music. MDMA (3,4-methylenedioxy-methamphetamine) is the active compound in XTC. Melatonin, the hormone of the night, is essential in the timing of sleep. Since MDMA causes hyperactivity and long-term sleep disturbances, a connection between MDMA and melatonin is easily made. There is a lack of studies that seek for a direct connection between MDMA and melatonin. Since the amount of MDMA-users tends to increase worldwide, more and more studies about its possible (negative) short- and long-term aftereffects show up. Acute effects of MDMA are an increased release of serotonin (5-HT), inhibition of 5-HT reuptake and stimulation of 5-HT neurons by being a 5-HT-receptor agonist itself. Also, MDMA mediates the dopaminergic- and adrenergic system via direct stimulation of the dopamine D2-receptor and a MDMA-mediated release of extracellular norepinephrine. It is shown that MDMA-induced long-term effects are degradation of 5-HT neurons, swollen (dysfunctional) 5-HT axons, constant lowering of 5-HT levels and a loss of 5-HT terminals in many brain regions. Long-term dysfunction of the suprachiasmatic nucleus (SCN) caused by MDMA is shown *in vitro* and may be due to this loss of 5-HT terminals. The SCN is responsible for the timing of sleep and the 24h rhythm in humans. The SCN is shown to re-entrain worse to nonphotic stimuli long after MDMA-usage, compared to a control. This dysfunction may be the cause of the sleep disturbances, as seen in severe MDMA-users. Also, an irreversible inhibition of the enzyme tryptophan hydroxylase (TPH) is found to be MDMA-mediated. TPH is an essential and rate-limiting enzyme in the synthesis of 5-HT and may therefore be the cause of the MDMA-mediated long-term lowering of 5-HT. Melatonin is synthesized from 5-HT. This paper therefore makes the assumption that a depletion of melatonin, as a result of the lowered 5-HT levels, may be the case in heavy MDMA-users. Due to its neuroprotective, antioxidative properties, oral melatonin administration may be an effective way to inhibit the 5-HT neurodegeneration caused by MDMA as well. Also, melatonin is shown to have the ability to phase shift the SCN and may therefore reduce the degraded activity of the SCN caused by MDMA.

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Introduction

Ecstasy (XTC) is a drug which is used worldwide, especially in the party scene. MDMA (3,4-methylenedioxy-methamphetamine) is the active compound in XTC and is substituted to the amphetamine class of drugs. MDMA tends to give its users a warm, tendering feeling. Also, users report to have more energy and a need to dance. Furthermore, MDMA-use is associated with increased energy and hyperactivity (Schierenbeck et al., 2008). This, and an increased sensitivity to music and lighting that comes with the usage of MDMA, explains the frequent use of this drug in the party scene (Generation Ecstasy, 1999).

Just like most amphetamine-classed drugs, one of the direct effects of MDMA is a reduction of sleepiness and induction of activity. Many severe MDMA-users report that this hyperactivity is still noticeable long after usage. Blagrove and colleagues (Blagrove et al., 2010) showed long-term alterations in motor activity and sleep in rats.

In November and December 2013 the biggest drug use survey in history was conducted. Almost 80.000 young people (most of them 20-30 years) from 17 different countries filled in an anonymous online questionnaire about their drug use that year. Although this questionnaire does not represent the entire population of these countries, since mostly young, well educated people participated, the report concluded that on average 23.4% of the sampled population had used MDMA that year (Global Drug Survey, 2014). The Trimbos-institute shows an increase in the last decade of young people who have ever used XTC or MDMA in their life in the Dutch population (age: 15-64 years) (Trimbos-intituut, 2014). Although the sample participants do not represent the entire Dutch population, an increasing trend of overall MDMA or XTC-usage is reported (Table 1).

	1997	2001	2005	2009
Ever use	2,3%	3,2%	4,3%	6,2%
Last year	0,8%	1,1%	1,2%	1,4%
Last month	0,3%	0,3%	0,4%	0,4%

TABLE 1: Percentage of the Dutch population (age: 15-65 yr) who report to have either ever used XTC or MDMA, have used it last year, or last month (N=17590 (1997); N=2312 (2001); N=4516 (2005); N=5769 (2009)) (Trimbos-instituut, 2014).

In 1914 MDMA was patented and an investigation to the potential medicinal usage began. So far, mainly the short-term effects of MDMA are investigated and reported, most of them *in vitro* or in experimental animals. But, since the recreational use of MDMA increased the last decades, also possible long-term effects of MDMA get the attention of researchers (Green et al., 1995).

Most of the MDMA-mediated effects in humans are found to be due to serotonergic innervation. An acute release of serotonin (5-HT) and direct stimulation of 5-HT-receptors by MDMA are at the basis of this innervation. A reported long-term effect of MDMA-usage, however, is a 5-HT depletion in the forebrain (Parrott et al., 2002). (See: Pharmacological effects of MDMA)

Melatonin (5-methoxy-N-acetyltryptamine) is a hormone found in both animals and humans. Melatonin shows a clear circadian pattern. Levels of melatonin are high during the dark phase of the light-dark cycle and hardly detectable during the light phase. Melatonin is an important factor in the entrainment to the light-dark cycle in mammals. Human circadian-rhythms can be shifted by oral

melatonin administration (Lewy et al., 1992). The suggestion that melatonin is a sleep inducing hormone is most likely wrong, since night-active (nocturnal) mammals react in another (opposite) way to melatonin than diurnal mammals. Therefore, melatonin as "a chemical expression of darkness" (Reither et al., 1991) is a better way to describe its general function. Due to its influence on sleep timing, melatonin is often administrated orally. Especially since oral administration of melatonin is a very effective way to increase serum melatonin levels and seems to have no major toxic effects (Waldhauser et al., 1984). Besides taking part in the entrainment to the light-dark cycle, melatonin seems to interact with the regulation of blood pressure, retinal physiology, seasonal reproduction, ovarian physiology, immune function and in inducing osteoblast differentiation (Altun et al., 2007). Melatonin is also found to be a strong antioxidant. Even its metabolites seem to be strong antioxidants (Dun-Xian Tan et al., 2006). Moreover, local melatonin synthesis correlates with lower neuronal death and is therefore found to be a neuro-protector (Pinato et al., 2015). This neuroprotective role of melatonin is shown to be due to its antioxidative properties. Peripheral tissue expresses melatonin receptors and can therefor explain the numerous functions of melatonin. These receptors are found in e.g.: SCN, retina, many aspects of the cardiovascular system and in prostate and breast (Ekmekcioglu et al., 2006). Therefore, Ekmekcioglu and colleagues concluded that these receptors are found almost everywhere in the human body. Although these receptors are so much found, the functional role of melatonin in humans remains partially unclear (Ekmekcioglu et al., 2006).

Melatonin is synthesis mainly in the pineal gland. 5-HT is synthesized from amino acid tryptophan and melatonin then again from 5-HT (See: Biosynthesis of Serotonin and Melatonin). The sleep disturbances that are shown in severe MDMA-users, may therefore well be due to the long-term depletion of 5-HT. After all, melatonin is synthesized from 5-HT. This paper makes the connection between MDMA and melatonin and answers the question whether (severe) MDMA-usage could lead to a depletion of melatonin. In addition, the possibilities of melatonin as a reducer of neurodegeneration is investigated. Could oral melatonin administration be a reducer of the neurotoxic and behavioral aftereffects of MDMA-usage?

Pharmacological effects of MDMA

The major effects of MDMA are the provocation of an increase of extracellular brain serotonin (5-HT) and an inhibition of the reuptake of 5-HT and thereby indirectly the stimulation of the numerous 5-HT-receptors. This is shown *in vivo* and *in vitro* (Nichols et al., 1982; Rudnick et al., 1992). Besides being a 5-HT releasing factor, MDMA directly stimulates the 5-HT_{2A}-receptor and the dopamine D2-receptor (Kehr et al., 2011), and causes an increase in extracellular dopamine and norepinephrine levels in the brain. Some of the 5-HT releasing effects of MDMA are due to interaction with the serotonin-transporter (SERT) (Liechti et al., 1999; Hasler et al., 2009). Monoamine oxidases (MOA's) are enzymes that catalyze the oxidation and thus the degradation of monoamines. 5-HT is mainly broken down by MAO A. MDMA is found to inhibit the production of MAO A in particular, hence increasing the extracellular 5-HT (Leonardi et al., 1994).

The acute (neurotoxic) effects of MDMA

The short-term neurotoxic effects of MDMA use are well known and described in many studies. The physiological neurotoxic effects are mainly manifestations of the so-called serotonin syndrome. This serotonin syndrome consists of symptoms that come with the increased levels of extracellular 5-HT and the inhibition of the enzyme complex MAO A in the central nervous system (Sternbach et al.,

1991). These symptoms vary from mild symptoms as a compelling need of moving (Akasthisia) and tremor, to life-threatening toxicity, which can ultimately lead to death (Figure 1) (Boyer et al., 2005).

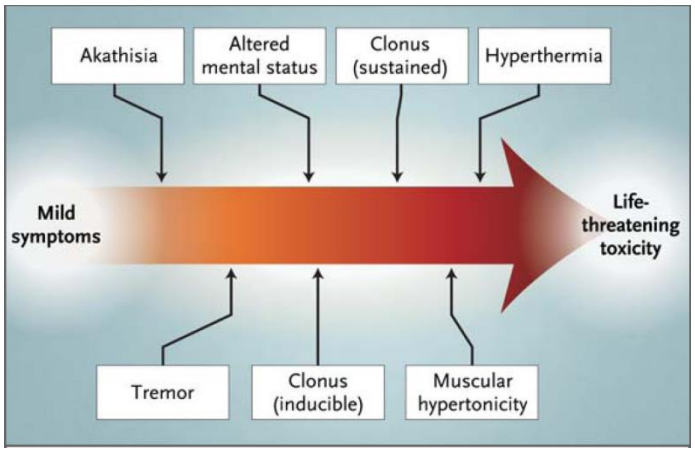

FIGURE 1: The symptoms of serotonin syndrome, observed in humans. These symptoms vary from mild symptoms to life-threatening toxicity and may ultimately lead to death (Boyer et al., 2005).

The sub-acute and long-term effects of MDMA

A lowering in mood, two to five days after the XTC or MDMA-usage, is reported by many users. Since XTC and MDMA are often used in weekends, people refer to this lowering in mood as "the mid-week blues", also "the Tuesday dip" is a commonly used term. Almost 80% of the users report this mid-week blues, as well as an impairment of their concentration (Verheyden et al., 2003). Parrott and colleagues (Parrott et al., 2002) reported a temporary depletion of 5-HT, due to MDMA-usage, in humans. Multiple effects of MDMA cause this depletion. Partly it is the result of the acute release of 5-HT by MDMA. Moreover, MDMA induces an irreversible inhibition of the enzyme tryptophan hydroxylase(TPH). TPH is an essential enzyme in the synthesis of 5-HT out of precursor tryptophan (see: 'Biosynthesis of serotonin and melatonin'). Another important cause of the temporary depletion of 5-HT is the MDMA-induced blockade of SERT activity(Meyer et al., 2013). Since 5-HT neurotransmission might mainly underlie depression-like behavior, the mid-week blues may be due this temporary depletion of 5-HT (Blier et al., 1994).

Occasional and low-dose use of MDMA has this earlier mentioned temporally sub-acute depletion of 5-HT. However, excessive or heavy(high-dose) usage of MDMA shows some long-term effects. The responsiveness to MDMA partially diminishes after usage (Parrott et al., 2005). This diminishment of response to the drug is called tolerance. Also, some studies have shown long-term mood effects of MDMA. Heavy MDMA-usage tends to correlate with an increased chance of having a depression or becoming depressed (Green et al., 1995). However, the causation of this correlation is hard to appoint. Since either the MDMA-usage causes this increase in the development of depression, or having a depression causes an increase in the chance to potentially use MDMA.

The long-term mood effects of MDMA-usage may be due to the neurotoxicity of MDMA. This neurotoxicity of MDMA seems to effect especially the serotonergic system. Green et al. reviewed that irreversible damage to 5-HT neurons is found (Green et al., 1995). Swollen axons and a reduction in 5-HT-terminals were found after MDMA usage in mice (Ohearn et al., 1988; Figure2) and long term loss of 5-HT neurons is shown in primates and mice after injecting MDMA(Green et al., 1995). The underlying neurotoxic mechanisms of MDMA are still in discussion, but are thought to be due to its pro-oxidant reactive metabolites (Barbosa et al., 2011). Also, many studies had shown that high

doses of MDMA may lead to 5-HT depletion in forebrain areas, particularly striatum, cortex and hippocampus (Green et al., 1995). This depletion of 5-HT in the forebrain may also induce effects on, for instance, the melatonergic system, since melatonin is synthesized from 5-HT.

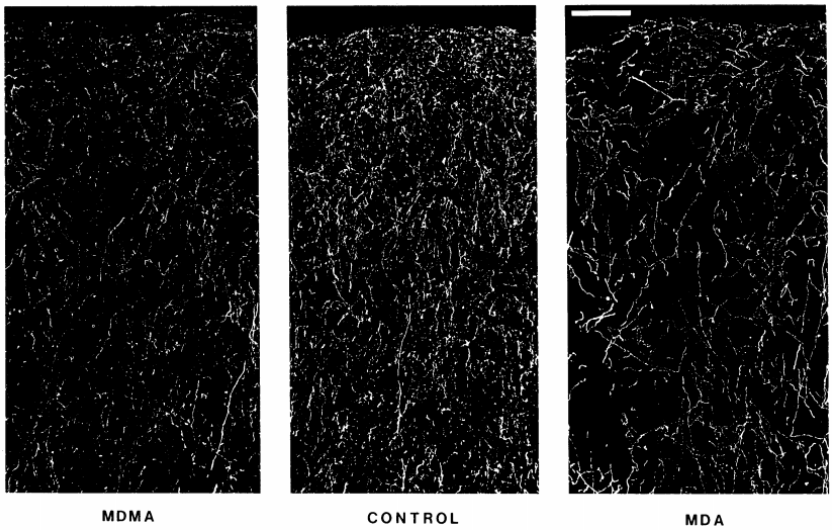

FIGURE 2: 5-HT-axon degeneration in the frontal cortex is seen in rats treated with MDMA or MDA (the metabolite of MDMA). This is pictured using 5-HT immunecyto-chemistry. The animals received either 8 doses (20 mg/kg) of MDMA, MDA or a control substance (Ohearn et al., 1988).

Effects of MDMA on sleep and circadian rhythms

Just like most amphetamine-classed drugs, one of the direct effects of MDMA is a reduction of sleepiness and induction of activity. Balogh et al. investigated whether the MDMA-induced wakefulness and motor activity would remain and detectable three weeks after a MDMA-injection in rodents. Most of the investigated parameters returned to normal, but alterations in deep slow wave sleep and motor activity were still found after three weeks (Balogh et al., 2004). These deep slow wave sleep alterations consisted of a significant increase in stage 3 and 4 sleep (Ricaurte et al., 2001). The amount of deep sleep and the regulation of sleep timing is thought to be organized by the interaction of two processes: a homeostatic process related to the duration of wakefulness and sleep and a circadian process originating in the circadian pacemaker: the suprachiasmatic nucleus (SCN) (Daan & Beersma 1984). The SCN receives inputs from the retina, the lateral geniculate nucleus, and the serotonergic neurons within the raphe nuclei(McCann et al., 2007). The SCN generates 24h rhythms and it can be entrained by e.g. light, melatonin or 5-HT input. McCann and colleagues (McCann et al., 2007) reviews a few studies done by Biello and colleagues (Biello et al., 2001, 2002, 2003; Gardani et al., 2005) in which the capability of MDMA to influence the SCN in animals is tested. In these studies it is concluded that MDMA attenuates the ability of the SCN to phase shift *in vivo* and *in vitro* (Figure 3). Furthermore Biello et al. found the 5-HT axon terminals degradation of MDMA to be the cause of cause of this impairment in response to the endogenous circadian clock, since the SCN contains these terminals. This is shown both *in vivo* and *in vitro* as well (Biello et al., 2001, 2002, 2003; Gardani et al., 2005). This phase shifting ability of the SCN is attenuated in response to both nonphotic stimuli (Triazolam) and light by the MDMA. Melatonin is found to phase shift the SCN as well. Therefore, the assumption of a reduction of melatonin induced phase shifting in MDMA-users, could well be made. No studies about this possible effect, however, is ever done.

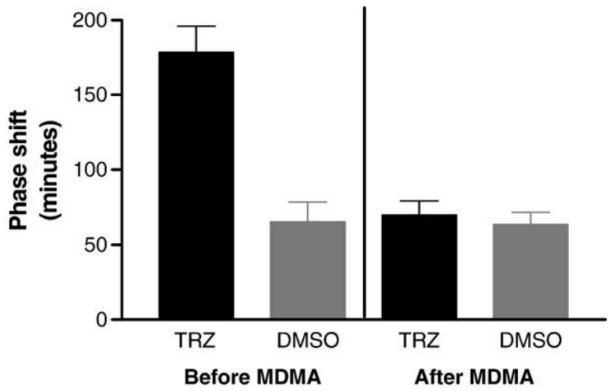

FIGURE 3: Triazolam(TRZ) is found to mediate an advanced phase shift of the SCN and thereby the running wheel activity pattern. Dimethyl sulfoxide(DMSO) is used as a vehicle. After MDMA-injection, the phase shift of the SCN attenuated (Gardani et al., 2005).

MDMA is associated with several memory deficits. Frequent MDMA-users (people who use at least twice a month) seem to have a deficit in declarative memory, which is one of the two long-term memory types (Blagrove et al., 2010). This may partially be due to the reduction of sleep latency, which is an acute effect of MDMA-usage, since sleep deprivation impairs memory capability (Schierenbeck et al., 2008). Furthermore, MDMA seems to provoke disturbances in sleep and in REM-sleep specifically (Randall et al., 2009). Also, MDMA seems to increase the risk of sleep apnea (McCann et al., 2009). The discrimination between these two memory deficit inducing factors was made by Kuypers et al., who showed that this memory impairment was not just due to deficiency of sleep, but an interaction between sleep deprivation and the MDMA usage. The memory capacity was measured four times during the night, either after MDMA administration or placebo. An impairment of memory capacity was shown in all participants, but the MDMA-group performed significantly worse. Kuypers and colleagues concluded therefore that MDMA increases the memory impairing effect of sleep deprivation (Kuypers et al., 2008).

The synthesis and metabolism of melatonin

Mammalian melatonin is secreted by the pineal gland. Exposure to light reduces melatonin levels in plasma and saliva. These non-image-forming effects of light can be explained by melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGC), which have a peak sensitivity at approximately 480 nm (Pierson et al., 2009; Dacey et al., 2005). In light-conditions these ipRGC-cells are hyperpolarized, which inhibits the release of norepinephrine. Though in darkness, these ipRGC-cells start to fire and mediate the melatonin production largely by postganglionic retinal nerve fibers. These fibers go through the retinohypothalamic tract to the SCN, then to the superior cervical ganglion and finally to the pineal gland (Figure 3). The activated sympathetic neurons mediate an increase of β1-adrenergic receptors in the pineal gland, a G protein-coupled cascade is activated and therefore an indirect stimulation of the production of melatonin is set(Brzezinski et al., 1997)(see: “Biosynthesis of Serotonin and Melatonin”). When synthesized, plasma melatonin levels start to rise quickly due to passive diffusion. These plasma levels are highly individual and age-dependent.

As mentioned before, peripheral tissues express melatonin receptors and are thereby influenced or entrained to the melatonin cycle. Melatonin is mainly metabolized in the liver. Nearly directly after being metabolized, the metabolite (6-sulfatoxymelatonin) is found in the urine, closely paralleling the serum melatonin levels (Brzezinski et al., 1997).

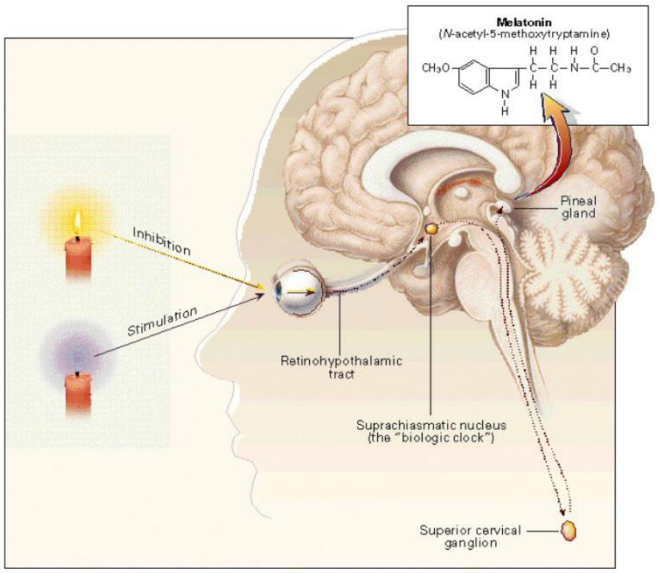

FIGURE 3: Inhibition and stimulation of melatonin production. Light inhibits the melatonin production, in total darkness melatonin production is maximal. (Brzezinski et al., 1997)

Effects of melatonin on sleep and circadian rhythms

As mentioned before, melatonin is often referred to as 'the sleep hormone'. Van de Werken et al. concluded that this is not right and all the found correlations between melatonin and melatonin-induced sleepiness were based on the coincidence that melatonin is high during sleep (van de Werken et al., 2013). This could well be the case. The closing of the eyelids while asleep simulates a constant darkness. Therefore the retina is not stimulated by light, the light-induced inhibition stops and melatonin production begins. A connection between an increase of sleepiness and a lowering of vigilance and high melatonin levels during the night are still under discussion. But during subjective daytime, exogenous melatonin induces sleepiness and can, depending on its timing, either advance or delay the human circadian clock and thus the timing of sleep (Arendt et al., 2004). Brzezinski summarized all literature that linked the many aspects of sleep, like sleep timing, latency, efficiency and sleepiness to exogenous melatonin in 1997 (Table 2).

Study	Year	Subjects	Administration of Melatonin		Effects
			Dose and Route	Timing and Duration	
Cramer et al.[39]	1974	15 normal subjects	Single dose of 50 mg intravenously	At 9:30 p.m.	Decreased sleep-onset latency
Vollrath et al.[40]	1981	10 normal subjects	Single dose of 1.7 mg intranasally	During daytime	Induction of sleep
Lieberman et al.[41]	1984	14 normal subjects	Total dose of 240 mg intravenously (80 mg given three times over a 2-hr period)	During daytime	Reduced alertness, increased fatigue and sleepiness
Dahlitz et al.[42]	1991	8 patients with delayed-sleep-phase syndrome	Single dose of 5 mg orally	At 10 p.m., for 4 wk	Earlier onset of sleep and wake-up time
Haimov et al.[43]	1995	26 elderly subjects with insomnia	Single dose of 2 mg orally (sustained release in one group and fast release in another)	2 Hr before bedtime for 1 wk	Increased efficiency and duration of sleep in sustained-release group, improved initiation of sleep in fast-release group
Garfinkel et al.[44]	1995	12 elderly subjects with insomnia	Single dose of 2 mg orally, controlled release	At night for 3 wk	Increased efficiency of sleep, no effect on total sleep time
Oldani et al.[45]	1994	6 patients with delayed-sleep-phase syndrome	Single dose of 5 mg orally	For 1 mo	Advanced onset of sleep
Dollins et al.[15]	1994	20 young subjects	Single dose of 0.1 or 0.3 mg orally	At midday	Increased duration of sleep, decreased sleep-onset latency
Zhdanova et al.[46]	1995	6 young subjects	Single dose of 0.3 or 1.0 mg orally	At 6, 8, or 9 p.m.	Decreased sleep-onset latency, no effect on REM sleep
Wurtman and Zhdanova[47]	1995	9 elderly subjects with insomnia	Single dose of 0.3 mg orally	30 min before bedtime	Increased efficiency of sleep, decreased sleep-onset latency

*All studies except that by Oldani et al. were placebo-controlled. REM denotes rapid eye movement.

Table 2:Litareture from experiments done between 1974 and 1995, which found a connection between the different aspects of sleep and exogenous melatonin.

These data may suggest that melatonin could be used as a chronobiotic to improve sleep, due to its advancing or delaying sleep timing effects. Indeed, melatonin has been reported to be successful in the treatment of some sleep disorders that are connected to abnormal timing of the circadian system. These disorders include sleep problems that come with a jetlag, shiftwork or the delayed or advanced sleep phase syndrome (Arendt et al., 2005). Jan et al. showed an important role of melatonin in the treatment of severe sleep disorders in children. After treated with oral melatonin, their sleep behavior improved (Jan et al., 1994).

Biosynthesis of Serotonin and Melatonin

Essential amino acid tryptophan (Trp) has a key role in both the synthesis of 5-HT and melatonin. There are many dietary sources that contain Trp, like bananas, oats, cheese and eggs. Consuming dietary sources that contain Trp is essential, since Trp cannot be synthesized by humans. 5-Hydroxytryptophan(5-HTP) is synthesized from Trp, catalyzed by the enzyme tryptophan hydroxylase (TPH). After this, 5-HT is synthesized from 5-HTP, catalyzed by aromatic amino acid decarboxylase (AAAD). 5-HT is essential in the synthesis of melatonin. From 5-HT, melatonin can be synthesized in two ways, either via catalyzation of hydroxyindole *O*-methyltransferase(HIOMT) in the first place and then via *N*-acetyltransferase (NAT) or the other way around. HIOMT *O*-methylizes the 5-HT in 5-Methoxytryptamine(5-MT). After this, melatonin is formed via *N*-acetylation from 5-MT, catalyzed by NAT. Also, 5-HT can be catalyzed by NAT in the first place, after which the intermediate N-Acetyl serotonin (NAS) comes. After this, melatonin is synthesized (Dun-Xian Tan et al., 2006)(Figure 5).

As mentioned before, melatonin is mainly synthesized in the pineal gland. However, studies have shown that tissue, other than the pineal gland, have the capability to synthesize melatonin as well. Pinato et al. reviewed very recently that melatonin could, besides in the pineal gland, be produced in several organs, including the retina, the gastrointestinal tract, immune competent cells and astrocytes in culture (Pinato et al., 2015).

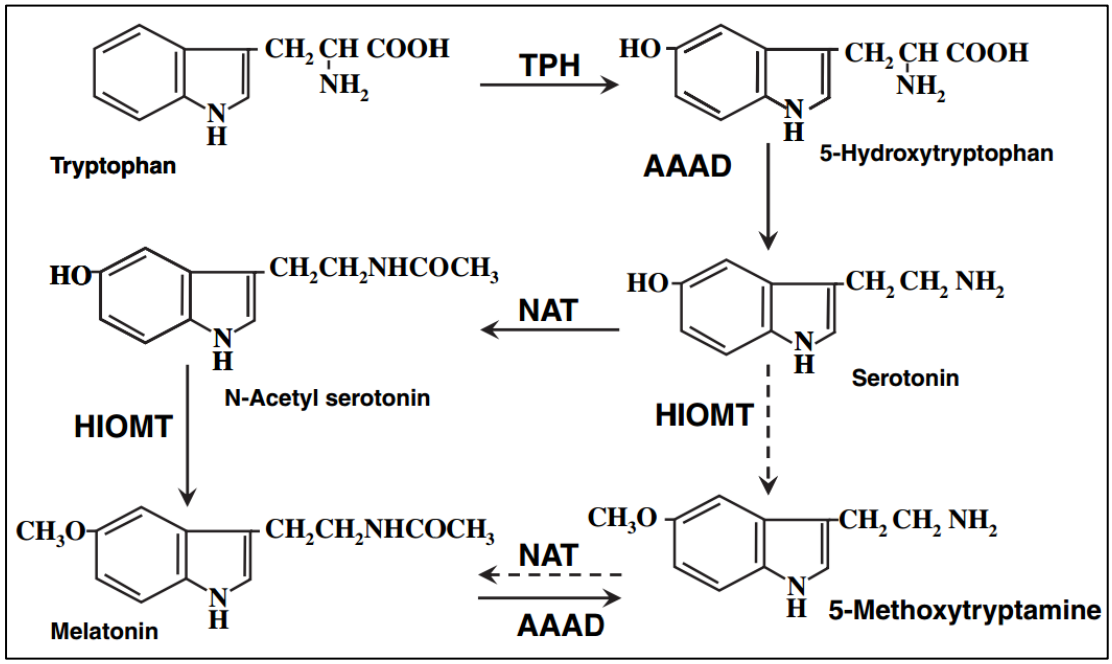

FIGURE 5: Biosynthesis of both melatonin and serotonin from Trp. Abbreviations : TPH= tryptophan hydroxylase; AAAD= aromatic amino acid decarboxylase; NAT= N-acetyltransferase; HIOMT= hydroxyindole 0-methyltransferase (Dun-Xian Tan et al., 2006).

Rate-limiting enzymes in the biosynthesis

The overall rate of an enzymatic reaction, and thus also in the synthesis of both serotonin and melatonin, is determined by the slowest step. In such reactions, the slowest step is often the activity of the enzyme which catalyzes the reaction. This enzyme is called the rate-limiting enzyme. In the short metabolic pathway to 5-HT, TPH is the rate-limiting step and thereby the most important enzyme concerning the rate of 5-HT synthesis. TPH has mainly been detected in the brain stem and in enterochromaffin cells in the gut (Walther et al., 2003). HIOMT activity is positively related to the melatonin production, and thus seen to be the rate-limiting enzyme in the synthesis of melatonin from 5-HT.

Potency of oral melatonin as a reducer of the aftereffects of MDMA-usage

Since (heavy) MDMA-usage may lead to a long-term depletion of 5-HT in the forebrain and several other areas of the brain, and melatonin is synthesized from 5-HT, the assumption of a MDMA-usage-induced depletion of melatonin can be made. Also, chronic or heavy MDMA-usage leads to the irreversible inhibition of the enzyme TPH, which is also an essential and rate-limiting enzyme in the synthesis of melatonin. This ultimately leads to the question: does chronic or heavy MDMA-usage lead to a depletion of melatonin in humans? If so, oral melatonin administration could be an effective way to counteract some of the negative neurotoxic and behavioral long-term effects of heavy or chronic MDMA-usage.

Conclusion and speculations

MDMA is a recreational drug which is used across the world, especially in the party-scene. The number of people who have used MDMA is rising. Although users report many acute positive effects, the negative aftereffects of MDMA-usage more and more show up in new studies. These studies confirm the negative impact both on the individual and for society of the trend of the increasing amount of MDMA-users worldwide. Although the assumption of a MDMA-induced melatonin shortage is easy to make, very little literature is found on this. The same applies to melatonin as a possible counteractive tool of these negative effects. The assumption of a connection between some of these negative long-term side-effects of heavy MDMA-usage and melatonin depletion can be made. Furthermore, it may be interesting to investigate whether oral administration of melatonin could counteract the neurotoxic effects of MDMA. An enumeration of all found (neurotoxic) effects of MDMA and the opportunities of melatonin as an inhibitor of these effects:

The neurotoxic effects of MDMA on 5-HT neurons

The long-term effects of MDMA on 5-HT neurons are overwhelmingly found in the literature. MDMA seems to induce swollen axons, the loss of 5-HT terminals and most importantly the loss of 5-HT neurons in various regions of the brain. This neurotoxic damage caused by MDMA is found to be due to the pro-oxidative properties of its metabolites. Melatonin, on the other hand, is found to be a very strong antioxidant. Even its metabolites seem to inhibit the oxidation of other molecules. This antioxidative nature of melatonin explains its neuroprotective property. Therefore, it can be hypothesized that melatonin has the possibility to reduce these neurotoxic effects caused by MDMA.

The effects of MDMA on 5-HT levels in the brain

The acute effects of MDMA are an increase in 5-HT levels in the brain and a stimulation of 5-HT neurons. This stimulation is due to self-innervation of the 5-HT receptors by MDMA, interaction with the re-uptake mechanisms of 5-HT (SERT) and its 5-HT releasing effects. On the other hand, the long-term effect of MDMA is a depletion of 5-HT in many regions of the brain. This is partially due to its acute releasing effects of 5-HT but also to irreversible inhibition of TPH and the loss of 5-HT neurons, caused by MDMA. 5-HT is crucial in the synthesis of melatonin as well, since melatonin is synthesized from 5-HT. Since TPH is the limiting enzyme in 5-HT synthesis and therefore in melatonin synthesis as well, inhibition could well cause a depletion of both. All these mentioned effects of MDMA lead to the assumption that MDMA could cause a deficiency of melatonin.

The negative effects on sleep and sleep timing

Acute effects of MDMA on sleep are an increased motor activity, restlessness and sleep apnea. Although some studies show long-term alterations in different sleep stages, a connection between melatonin and differences in sleep stages is not made. MDMA is shown to reduce the capability of the SCN to re-entrain to nonphotic input. This is speculated to be due to the reduction of 5-HT terminals in the SCN, due to severe MDMA-usage. Since melatonin is found to be a zeitgeber to the SCN and therefore has the capability of altering the timing of sleep in an effective way, oral melatonin administration could partially diminish these negative long-term effects of MDMA-induced neurotoxicity.

Discussion and a design for future studies

Nearly all these studies can be criticized; since most of them are done in animals. The assumption that the conclusions also applies to humans could be wrong. For example melatonin is found to partially have another (opposite) function in humans compared to some of its functions in some (nocturnal) animals (Reiter et al., 1991). Just like melatonin, MDMA could have different effects on the human brain, compared to that of an animal. Though it still is interesting to look for a connection between (severe) MDMA-usage and melatonin depletion or melatonin as a reducer of MDMA-induced long-term effects. Also, the people who participated in the human-based studies are likely to be poly-drug users, which makes it hard to exclude the results caused by other drugs or an interaction between drugs.

Future studies in finding this probable connection between melatonin and MDMA-usage, should first focus on the question whether (severe) MDMA-usage could lead to depletion in melatonin. Since plasma melatonin levels differ much inter-individually and are age-dependent, plasma melatonin levels should be measured before participants are exposed to MDMA. Like this, the comparison can be made and the direct and long-term effect of MDMA-usage on plasma melatonin levels can be determined. A lack of information makes it therefore hard to investigate the effects of severe MDMA exposure in humans, since plasma melatonin levels before this exposure are not available in most cases. Therefore, these studies will be animal-based.

Also, it is interesting to investigate whether oral melatonin administration could inhibit the acute neurotoxic effects of MDMA. Via a PET-scan, the loss of 5-HT-terminals, 5-HT neurons and 5-HT levels itself can be investigated in the brain, with and without oral melatonin administration, and compared. Hereby the neuroprotective properties of melatonin can be linked to these severe 5-HT neuronal damage done by MDMA. This can either be done in humans or animals, although ethics in these human-based studies may be involved. In humans, activity patterns of brain areas can be determined in severe MDMA-users and compared to a control.

Furthermore, the assumption is made that melatonin could reduce the severe effects of MDMA on the main circadian pacemaker, the SCN. Responses of the SCN in the sense of re-entrainment to nonphotic- and light-mediated phase shifts, can be measured both *in vivo* and *in vitro* in animals. Since the effects of melatonin on sleep are still under discussion, melatonin administration as a possible treatment to the sleep deprivation, reported by severe MDMA-users, would be interesting to look at.

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