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Methylphenidate-induced motor activity in rats: modulation by melatonin and vasopressin

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Abstract

Methylphenidate (MPH), a dopamine (DA) reuptake inhibitor, is well known to enhance motor activity, in part depending on the time of its application during the light–dark cycle. Moreover, after MPH administration, the hypothalamo-neurohypophysial axis including the neuropeptide vasopressin (AVP) was found influenced. Both the latter and behavioural effects of central AVP can also be modulated by the pineal gland with its light–dark-dependent activity. The present study was performed to investigate whether the pineal gland, its hormone melatonin (Mel), and AVP are involved in the MPH-evoked stimulation of activity. After application of 10 mg/kg MPH, the motor activity in pinealectomised (PE) rats was significantly higher than in sham-operated (SO) animals. After application of 250 μg Mel before MPH treatment, the stimulation of motor activity was diminished in PE rats and augmented in SO animals; however, when SO and PE rats were compared after Mel pretreatment, the reaction to MPH was nearly identical. Blocking the endogenous AVP by 25 or 1 μg of the V1a receptor antagonist $d(CH_2)_5[Tyr(Me)^2]AVP$ (AAVP) before MPH treatment significantly augmented the motor activity in SO rats only and abolished the differences seen between SO and PE animals after MPH application. The present results indicate that the behavioural stimulation of MPH was modulated by both the pineal gland with its hormone Mel as well as the neuropeptide AVP.

Keywords: Ritalin; Methylphenidate; Motor activity; Pineal gland; Melatonin; Vasopressin; Behaviour; Rat

1. Introduction

The psychostimulant methylphenidate (Ritalin, MPH), while commonly prescribed for the treatment of attention-deficit hyperactivity disorder, is well known to enhance the motor activity in a dose-dependent manner (Gaytan et al., 1996; Gerasimov et al., 2000). The neurochemical mechanisms that underlie these therapeutic and stimulant properties have been attributed to an increase in the dopamine (DA) concentration by inhibition of the synaptic DA reuptake (Butcher et al., 1991; Hurd and Ungerstedt, 1989; Gatley et al., 1996; Kuczenski and Segal, 1997), but norepinephrine (NE) may also be involved in the MPH-evoked effects (Kuczenski and Segal, 2001). Moreover, the hypothalamo-neurohypophysial system was found influenced after administration of MPH (Appenrodt et al., 1997), thus vasopressin (AVP) and oxytocin (Oxy) levels were found altered. Yet, the neuropeptide AVP acting as a neurotransmitter or neuromodulator is well known to be involved in several behavioural performances (see Engelmann et al., 1996), e.g., in locomotor activity (Appenrodt and Schwarzberg, 1999; Günther et al., 1988); therefore, it is desirable to investigate whether such changes in central AVP level seen after MPH application may also be involved in the MPH-evoked enhanced motor activity.

Furthermore, in first findings, it was demonstrated that behavioural effects after MPH administration can vary as a function of the time of application during the light–dark cycle (Gaytan et al., 1997a, 2000); on the other hand, MPH can induce a circadian locomotor rhythm in suprachiasmatic nuclei-lesioned rats (Honma and Honma, 1992). These results give rise to the question of an at least indirect relationship between the pineal gland, an organ that is known to be critically involved in biological rhythms (Reiter, 1991), and the different behavioural effects of MPH seen during the light–dark cycle. In this respect, the

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pineal gland or its hormone, melatonin (Mel), have been reported to influence the metabolism of several neurotransmitters such as DA, NE, or serotonin (5-HT) (Alexiuk and Vriend, 1993a,b; Golombek et al., 1996; Khaldy et al., 2002; Miguez et al., 1996, 1997), which are known to be involved in motor activity, and similar effects were noted on central AVP and Oxy (Bojanowska et al., 1998, 1999; Forsling, 2000; Forsling et al., 1993; Isobe et al., 2000). Along the same lines, it was found that the alterations in central AVP and Oxy levels after MPH application are dependent on the application time during the light–dark cycle as well as the function of the pineal gland (Appenrodt et al., 1997). Moreover, several investigators have reported an implication of the pineal gland in some of the behavioural effects of central AVP (Appenrodt and Schwarzberg, 1999, 2000; Appenrodt et al., 2002; Juszczak et al., 1996, 1999). Hence, it is imaginable that a possible involvement of the pineal gland in different behavioural effects of MPH seen during the light–dark cycle could also include vasopressinergic mechanisms.

Therefore, in the present investigation, experiments were conducted (1) to determine whether or not the pineal gland is involved in the stimulation of motor activity after MPH administration and (2) to investigate the possible role of endogenous AVP during this behavioural stimulation. For this, a single dose of 10 mg/kg MPH was administered in pinealectomised (PE) as well as sham-operated (SO) rats and the motor activity was measured. To verify possible differences between PE and SO rats in further groups, the pineal gland hormone Mel was substituted for pinealectomy. Moreover, to reveal the role of AVP in PE and SO rats, an AVP-V1a receptor antagonist (AAVP) was given to block the endogenous AVP during MPH treatment.

2. Materials and methods

2.1. Animals

The animal experiments were performed in accordance with our authority guidelines after obtaining the permission of the Institutional Review Committee for the use of animals in experiments. Male Wistar rats (Harlan, Borchen, Germany), kept under a 12:12 h light–dark cycle (light on at 6:00 a.m.), were used; standard laboratory food and water were available ad libitum. The weight of the animals was

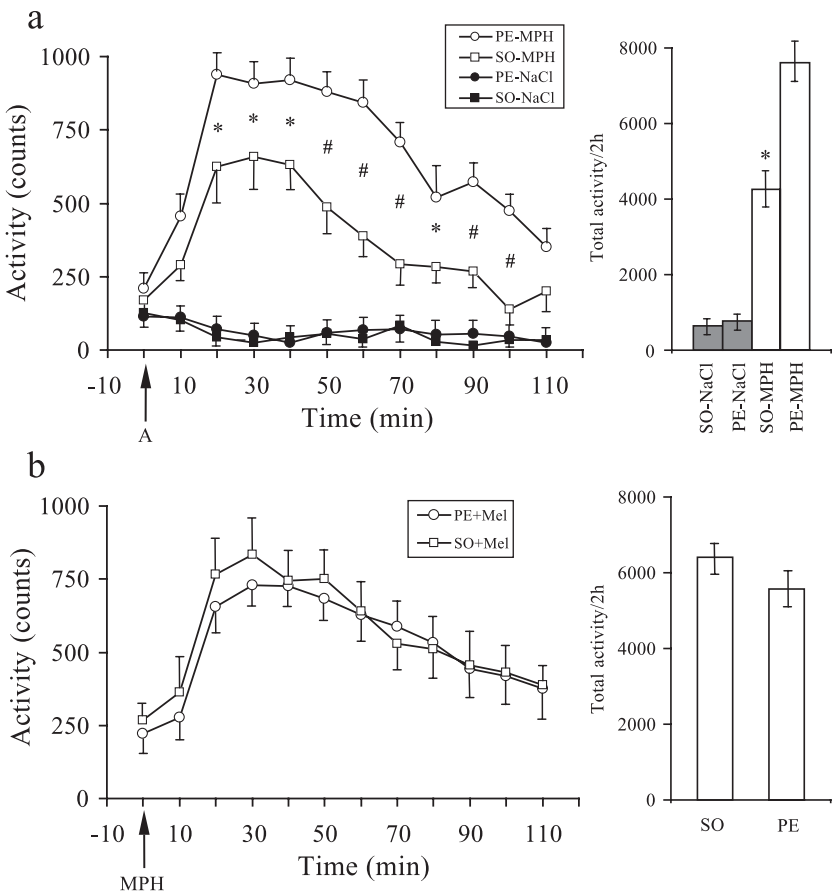

Fig. 1. (a) Activity (cumulated activity counts) in SO and PE rats after application (A) of 10 mg/kg MPH or 250 μl NaCl. The bar graph represents the total activity during the experimental time. The values are means ± S.E.M. (MPH: $n = 11$, NaCl: $n = 10$), * $P < .05$, # $P < .01$ (SO vs. PE). (b) Activity (cumulated activity counts) in SO and PE rats after application of 10 mg/kg MPH plus 250 μg Mel administered 10 min before MPH application. The bar graph represents the total activity during the experimental time. The values are means ± S.E.M. ($n = 11$).

approximately 160 g during pinealectomy and later, during substance application, between 280 and 340 g. The surgical procedures of pinealectomy or sham operation (virtually identical procedures, except that in the latter the pineal gland was not removed) were carried out under pentobarbital anaesthesia (60 mg/kg). After a recovery period of 3 weeks, both SO and PE rats were divided into following subgroups: MPH + NaCl (vehicle control), MPH + Mel, MPH + AAVP, and the respective control groups without MPH and housed individually in plastic cages. Upon completion of the experiments, the animals were killed by an overdose of pentobarbital, the skull was opened, and the pinealectomy verified.

2.2. Motor activity

The measurements were conducted in a noise-reduced room between 7:00 and 11:00 a.m., the animals being tested in their home cages (27 × 19 × 15 cm). The motor activity (locomotor, stereotyped behaviour, and other movements in total) was recorded at a 120-min time interval (every 10 min the counts were cumulated) by two motility meters based on a capacity procedure (TSE Mot V1.2, TSE, Bad Homburg, Germany). The observations were scheduled in a paired approach: one SO and one PE rat.

2.3. Drug administration

Mel (Sigma, St. Louis, MO, USA) was freshly dissolved in ethanol and 0.9% NaCl (5% ethanol) and 250 μg Mel in 250 μg solution applied subcutaneously (sc). The AVP-V1a inhibitor $d(CH_2)_5[Tyr(Me)^2]AVP$ (Sigma) was subcutaneously applied at doses of 25, 1, or 0.1 μg (in 250 μl 0.9% NaCl); MPH (Ritalin; Ciba-Geigy, Basel, Switzerland) was dissolved in 0.9% NaCl (10 mg/ml) and administered intraperitoneally (ip) at a dose of 10 mg/kg body weight of the rat.

2.4. Statistics

The data were expressed as mean values ± S.E.M. Statistical analysis was performed by the GLM procedure (SPSS software 9.0, SPSS 1999). Operation (SO, PE) and treatment (MPH, MPH + Mel, MPH + AAVP, and MPH + NaCl) were

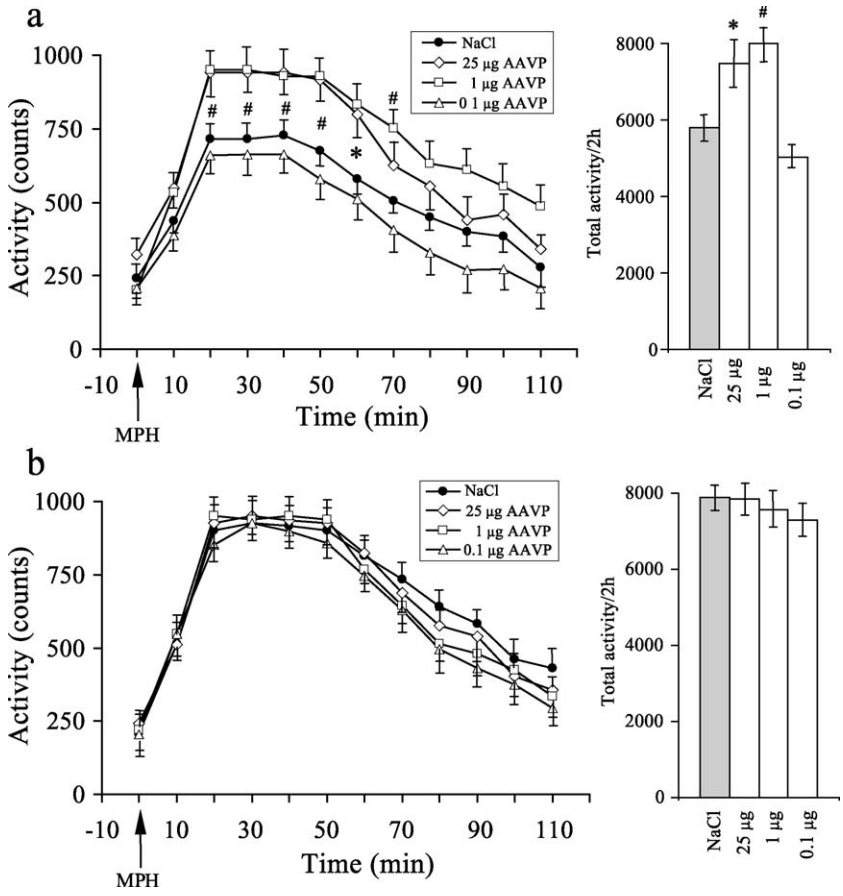

Fig. 2. (a) Activity (cumulated activity counts) in SO rats after application of 10 mg/kg MPH plus several doses of the V1a receptor antagonist (AAVP) or 250 μl NaCl administered 10 min before MPH application. The bar graph represents the total activity during the experimental time. The values are means ± S.E.M. (NaCl: $n = 24$; AAVP: 25 μg, $n = 10$; 1 μg, $n = 9$; 100 ng, $n = 7$), * $P < .05$, # $P < .01$ vs. NaCl control. (b) Activity (cumulated activity counts) in PE rats after application of 10 mg/kg MPH plus several doses of the V1a receptor antagonist (AAVP) or 250 μl NaCl administered 10 min before MPH application. The bar graph represents the total activity during the experimental time. The values are means ± S.E.M. (NaCl: $n = 20$; AAVP: 25 μg, $n = 11$; 1 μg, $n = 10$; 100 ng, $n = 7$).

set as fixed factors and the motor activity (time) as the dependent variable; repeated measures analysis was used for multiple comparisons (Time × Treatment, Time × Operation, between- and within-subject factors). Where a statistically significant main effect was found (tests of within- and between-subjects effects), post hoc comparisons were undertaken by a one-way ANOVA following the Dunnett *t* tests or the independent samples *t* test (after Levene's test for equality of variances); $P < .05$ was considered statistically significant.

3. Results

3.1. MPH and Mel treatment

The intraperitoneal injection of 10 mg/kg MPH increased the motor activity in SO as well as PE rats [tests of within-subjects effects: $F(1,39) = 34.4$, $P < .001$] with a maximum effect noted after about 30 min (Fig. 1a); however, statistical analysis revealed significant differences in the behavioural reaction between SO and PE rats [tests of between-subjects effects: $F(1,39) = 5.21$, $P = .028$] in that the increase in motor activity was augmented and prolonged in the PE animals [$F(1,18) = 17.3$, $P = .001$] (Fig. 1a). In accordance with these results, following MPH + NaCl administration (control group for AAVP application, Fig. 2a and 2b) also in the PE rats, the behavioural reaction was significantly enhanced [$F(1,42) = 14.24$, $P < .001$; Time × Operation interaction in the tests of within-subjects effects: $F(1,42) = 4.11$, $P = .039$]. Pretreatment of the rats with 250 μg sc of Mel 10 min before MPH application abolished the differences in motor activity seen between SO and PE groups after MPH application (Fig. 1b). Whereas in both groups, the Mel pretreatment significantly influenced the motor activity evoked by MPH administration, in SO rats, the behavioural reaction was augmented [$F(1,18) = 5.56$, $P = .03$] and in PE rats the activity was diminished [$F(1,19) = 4.52$, $P = .047$]. In both the SO and PE control groups, subcutaneous Mel application (Fig. 3) as well as intraperitoneal NaCl administration (Fig. 1a) were without effects on motor activity.

3.2. MPH and AAVP treatment

Following intraperitoneal injection of MPH plus subcutaneous application of 25 μg, 1 μg, or 100 ng AAVP (or NaCl), the statistical analysis revealed significant effects in the factors of time [$F(1,89) = 159$, $P < .001$], operation [$F(1,89) = 5.77$, $P = .018$], and treatment [$F(3,89) = 4.19$ $P = .008$]. Furthermore, a Time × Treatment interaction was found [$F(3,89) = 1.82$, $P = .039$]. In SO rats, the AAVP pretreatment clearly influenced the MPH-evoked elevated motor activity [$F(3,46) = 6.64$, $P = .001$; Time × Treatment interaction: $F(3,46) = 2.067$, $P = .015$] in that the behavioural reaction was significantly augmented after application of 25 and 1 μg AAVP, whereas the dose of 0.1 μg was without effect (Fig. 2a). In contrast to the SO rats in PE animals, the motor activity after MPH + AAVP treatment did not differ from the activity of the MPH + NaCl control group (Fig. 2b). The subcutaneous administration of AAVP without MPH did not produce an effect on motor activity in both SO and PE rats (Fig. 3).

4. Discussion

The results of the present study indicate that the pineal gland is involved in the MPH-evoked stimulation of motor activity. The observation that in PE rats the motor activity was more augmented than in pineal-intact controls is consistent with similar findings obtained in response to administration of the psychostimulant, amphetamine; that is, in PE

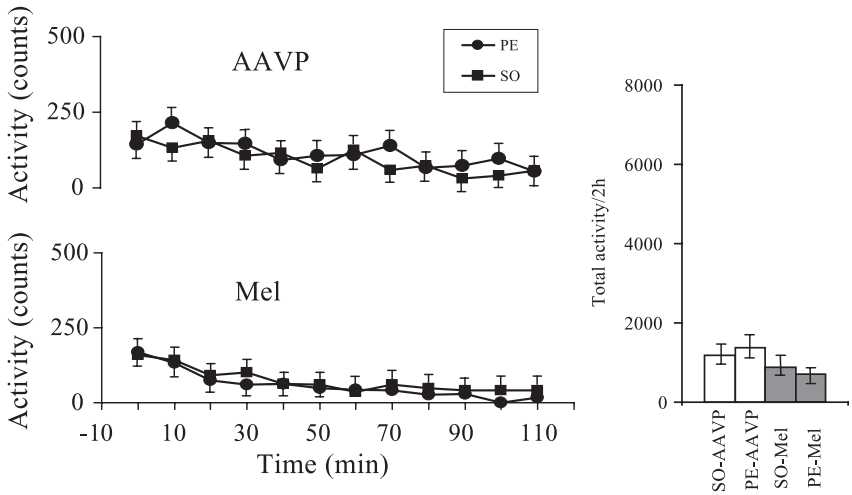

Fig. 3. Activity (cumulated activity counts) in SO and PE rats after application of 250 μg Mel or 25 μg of the V1a receptor antagonist (AAVP). The substances were administered at time 0. The bar graph represents the total activity during the experimental time. The values are means ± S.E.M. (Mel: $n = 7$, AAVP: $n = 8$).

rats even low doses produced a behavioural pattern, which resembled that noted after high doses, and this effect was restored after pineal gland transplantation (Palaoglu et al., 1994). These results are therefore of interest, given the similarity of the behavioural effects noted after application of the psychostimulants, MPH and amphetamine: low doses induce locomotor stimulation, high doses chiefly stereotyped activity (Fray et al., 1980; Roffman and Raskin, 1997; Swerdlow et al., 1993), and the neurochemical response profiles of both substances are comparable too (Kuczenski and Segal, 2001). The augmented motor behaviour seen after pinealectomy in response to both psychostimulants suggests an inhibitory effect of the pineal gland, and this seems to be mediated by its hormone, Mel, which is produced in a light–dark-dependent pattern. The latter assumption has been supported by the present finding that after Mel treatment, the MPH-evoked motor activity was reduced in PE rats and, moreover, comparison of PE and SO groups after Mel application revealed that the differences in motor activity after MPH administration were clearly abolished. As the circadian rhythm of pineal Mel synthesis has to be considered, that comparison in particular can be assumed as a control, for in both groups, a physiologically comparable situation that would normally exist in pineal-intact rats during the dark phase, viz., with maximum in Mel production, was mimicked. The finding that SO rats likewise exhibited a small influence of Mel on the activity stimulation in that the effect was intensified might be attributed to the fact that the present experiments were performed during the early light phase, i.e., in the SO rats with their intact circadian rhythm, a physiological situation with minimised Mel level and Mel-receptor sensitivity (Reiter, 1991), and not optimised for Mel effects.

The finding referred to above would seem to agree with the fact that nocturnal species like rats have their main activity during the night while the pineal Mel production increases to maximum. If the circadian setting of the animals were considered, then in behavioural experiments, a simple substitution of Mel application for pinealectomy as performed in the present investigation can be successful; the social memory after septal AVP infusion was found to be impaired in PE rats and after application of 250 μg Mel, the social memory was improved in PE animals in the same manner as in SO rats (Appenrodt et al., 2002). Those experiments were carried out at night (approximately 1 h after both lights off and Mel application), during the period when both pineal Mel production and Mel receptor sensitivity in SO rats increase to maximum. The observation that neither pinealectomy nor application of Mel alone influenced the motor activity suggests that the pineal gland and its hormone, Mel, are not basically involved in motor behaviour. However, the present results were indicative of an inhibitory effect of the pineal gland via Mel in the modulation of MPH-evoked behaviour, and this would seem to account for some of the different effects of MPH reported by other workers. For example, the development of sensitisation to MPH (i.e., augmented behavioural response after chronic treatment) (McDougall et al., 1999; Crawford et al., 1998; Gaytan et al., 1997b) was seen to be time dependent, with the most pronounced sensitisation occurring during the light phase, whereas no sensitisation was observed during the middle of the dark phase (Gaytan et al., 2000), i.e., during a period of maximum capacity of the pineal-gland Mel synthesis; likewise the behavioural effects noted after high doses of MPH varied between the light and the dark phase, with a smaller stereotypic effect seen during the dark (Gaytan et al., 1997a). Moreover, it was found that pinealectomy blocked the motor activation effect of injection stress and this effect was reinstated by Mel administration (Ruzich and Martin-Iverson, 2000). The aforementioned results support the suggestion of an inhibitory role of Mel during motor stimulation; in this context, given the neurochemical response to MPH treatment, an influence can be assumed to occur via aminergic neurotransmitters for relationships existing between Mel, and the latter are well documented in several mammalian brain areas. Typically, rhythmic changes of DA level in the mouse striatum were blunted by pinealectomy, whereas administration of Mel restored the rhythm (Khaldy et al., 2002). Moreover, it was found that Mel administration reduced NE synthesis in both neurointermediate lobe and brain stem of Syrian hamsters (Alexiuk and Vriend, 1993a,b).

Yet, several findings obtained by other workers and the outcome of further investigations in our laboratory imply that functional connections exist between the pineal gland and neuropeptidergic mechanisms. For example, both the hypothalamo-neurohypophysial system, including the AVP level (Appenrodt et al., 1997; Bojanowska et al., 1998; Forsling, 2000; Forsling et al., 1993; Isobe et al., 2000) and the effects of AVP on learning, memory, and locomotor behaviour (Appenrodt and Schwarzberg, 1999; Juszczak et al., 1996, 1999) were found influenced after pinealectomy or Mel treatment. In the present investigation as well, the stimulated motor activity was seen augmented after blockade of the endogenous AVP (by AAVP) in the SO rats only. This is consistent with further investigations into social memory

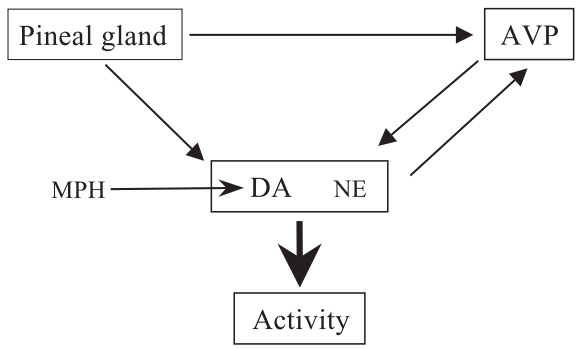

Fig. 4. Possible functional (inter)relationships between pineal gland, vasopressin (AVP), and aminergic neurotransmitters such as DA and NE during MPH-evoked stimulation of activity.

(Appenrodt et al., 2002) or anxiety behaviour (Appenrodt and Schwarzberg, 2000) in which the AVP effects failed in PE rats. With regard to the neurochemical effects of the stimulant MPH, the endogenous AVP can be assumed to yield an effect via modulation of aminergic mechanisms by analogy to the presumable effect of Mel. Other findings have been published suggesting that some of the behavioural effects of AVP can be mediated through aminergic neurotransmitters. Typically, it was reported that the preservation of social memory following AVP administration was abolished by olfactory bulb NE depletion (Dluzen et al., 1998) and, along similar lines, an enhanced memory consolidation in passive avoidance performance was abolished by 6-OHDA lesions of the ascending dorsal NE bundle (Kovács et al., 1979). AVP-induced flank marking in hamsters was inhibited by several 5-HT agonists (Albers et al., 2002), and there are other data indicating that the anxiogenic effect of high doses of AVP is inhibited by a dopamine D2 receptor antagonist (Bhattacharya et al., 1998). Earlier studies suggested that central AVP administration affect NE and DA metabolism in several brain areas (see Kovács et al., 1979). More recent results revealed that dendritically released AVP modulates NE release within the supraoptic nucleus in a bimodal fashion (Yamashita et al., 2001) and AVP increased the DA release in the striatum of water-deprived rats (Tyagi et al., 1998). Inversely, NE stimulates the AVP expression in the paraventricular and supraoptic nuclei (Vacher et al., 2002). Considering the fact that the behavioural effect of MPH has been mediated through biogenic amines and the metabolism of these transmitters can also be influenced by both the pineal gland hormone, Mel, and the neuropeptide, AVP, then these functional relations (Fig. 4) would seem to provide an explanation for the different MPH-evoked behavioural effects after AAVP and Mel application in PE and SO rats.

As MPH induces both locomotor stimulation and stereotyped activity at least partially on distinct neuronal pathways, it is still an open question if both responses were modulated in the same direction by Mel and AVP. Moreover, stronger conclusions might be reached with a broader dose–response analysis of the substances used, and in this respect it has to be considered that pinealectomy might alter MPH pharmacokinetics and initiate adaptive processes. Therefore, further investigations are necessary to reveal complex possibilities of behavioural modulation such as those ensuing from Fig. 4. Whether the physiological meaning of such a modulation is just an adaptation of the behavioural pattern during the light–dark cycle, or something beyond, is still an open question that should be elucidated.

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