Accumbal noradrenaline that contributes to the alpha-adrenoceptor-mediated release of dopamine from reserpine-sensitive storage vesicles in the nucleus accumbens is derived from alpha-methyl-para-tyrosine-sensitive pools

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Abstract Alpha-adrenoceptors in the nucleus accumbens are known to inhibit accumbal dopamine release from reserpine-sensitive pools. The aim of this study was to test our previously reported hypothesis that accumbal noradrenaline that controls the dopamine release from these storage vesicles is derived from alpha-methyl-para-tyrosine-sensitive pools. The sensitivity of accumbal alpha-adrenoceptors to noradrenergic agents depends on the amount of noradrenaline that is available in the synapse. In case the synaptic noradrenaline levels decrease, the conformation of alpha-adrenoceptors changes into a state that makes these receptors more sensitive to its agonists. The effects of alpha-methyl-para-tyrosine, respectively reserpine, on the alpha-adrenoceptor-agonist-induced changes of accumbal dopamine release were investigated. Alpha-methyl-para-tyrosine, but not reserpine, made accumbal postsynaptic alpha-adrenoceptors more sensitive to phenylephrine. These results indicate that noradrenaline that inhibits the release of dopamine from reserpine-sensitive storage vesicles, via stimulation of accumbal postsynaptic alpha-adrenoceptors, is derived from alpha-methyl-para-tyrosine-sensitive pools. The clinical impact of these data is discussed.

Keywords Alpha-adrenoceptors · Alpha-methyl-para-tyrosine · Noradrenaline–dopamine interactions · Norepinephrine–dopamine interactions · Nucleus accumbens · Reserpine

Introduction

It has been found that the sensitivity of alpha-adrenoceptors to noradrenergic agents depends on the amount of noradrenaline that is available in the synapse. In case the synaptic noradrenaline levels increase, the conformation of alpha-adrenoceptors change into a state that makes them less sensitive to agonists and more sensitive to antagonists (Cools et al. 1987, 1991; Tuinstra and Cools 2000a; Cools and Tuinstra 2003; Aono et al. 2007). The opposite holds also true: in case the synaptic noradrenaline levels decrease the conformation of alpha-adrenoceptors change into a state that makes them more sensitive to agonists and less sensitive to antagonists (Cools et al. 1987, 1991; Tuinstra and Cools 2000a; Cools and Tuinstra 2003). It is evident that these processes provide a homeostatic mechanism, controlling the adrenergic activity at postsynaptic receptors.

Alpha-adrenoceptors are known to control the release of dopamine. Both in vitro and in vivo experiments have revealed that stimulation of postsynaptic alpha-adrenoceptors that are located on dopaminergic neurons inhibits the release of dopamine in the nucleus accumbens, whereas inhibition of these receptors stimulates the release of dopamine in this brain structure (Nurse et al. 1984, 1985; Russell et al. 1988, 1993; Tuinstra and Cools 2000a; Cools and Tuinstra 2003; see also Verheij and Cools 2008). It is generally accepted that presynaptic alpha-adrenoceptors regulate the amount of noradrenaline in the synapse and, accordingly, regulate the amount of noradrenaline at the level of postsynaptic alpha-adrenoceptors. Interestingly, the noradrenaline agonist phenylephrine (PE) has been found to act at accumbal presynaptic, but not postsynaptic, alpha-adrenoceptors of otherwise untreated rats (Tuinstra and Cools 2000a,

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2000b; Cools and Tuinstra 2003; Aono et al. 2007; see also below). This action of PE has been found to reduce the synaptic noradrenaline levels (Aono et al. 2007), which, in turn, results in an increased release of accumbal dopamine in these rats (Tuinstra and Cools 2000a, 2000b; Cools and Tuinstra 2003). It has recently been demonstrated that the alpha-adrenoceptor-mediated release of accumbal dopamine is not derived from alpha-methyl-para-tyrosine (AMPT)-sensitive dopamine pools (Tuinstra and Cools 2000b; see also Verheij and Cools 2008). In fact, the alpha-adrenoceptor-mediated dopamine release is derived from reserpine (RES)-sensitive pools of dopamine (Cools and Verheij 2002; Verheij and Cools submitted; see also Verheij and Cools 2008). It is currently unknown which type of noradrenergic pool releases noradrenaline that inhibits accumbal dopamine release from these storage pools. On the basis of previously reported neurochemical data, however, it has been hypothesized that accumbal noradrenaline derived from AMPT-sensitive pools controls the alpha-adrenoceptor-mediated release of accumbal dopamine from RES-sensitive vesicles (Saigusa et al. 1999).

Given the fact that stimulation of postsynaptic alpha-adrenoceptors in the nucleus accumbens inhibits the release of accumbal dopamine (see above), the inability of the alpha-adrenoceptor agonist PE to decrease the amount of accumbal dopamine in otherwise untreated rats (Tuinstra and Cools 2000a, 2000b; see also above) has been ascribed to the presence of a relatively high amount of noradrenaline in the synapses of these rats (Tuinstra and Cools 2000a). Under these conditions it can be predicted that an experimentally induced decrease of the amount of synaptic noradrenaline makes the accumbal postsynaptic alpha-adrenoceptors sensitive to PE. AMPT is known to reduce the alpha-adrenoceptor-mediated release of noradrenaline (Brannan et al. 1991; McTavish et al. 1999).

In order to test whether the noradrenaline release at the level of postsynaptic alpha-adrenoceptors in the nucleus accumbens is derived from AMPT-sensitive pools, the effects of AMPT on the PE-induced accumbal dopamine release were established. Combining the above-mentioned considerations results in the hypothesis that AMPT makes the accumbal postsynaptic alpha-adrenoceptors sensitive to PE. It is hypothesized that PE decreases the amount of accumbal dopamine in AMPT-treated rats (postsynaptic action) in contrast to PE that will increase the amount of accumbal dopamine in control rats (presynaptic action). In order to establish whether RES-sensitive pools contribute to the release of accumbal noradrenaline at postsynaptic alpha-adrenoceptors as well, the effects of RES on the PE-induced accumbal dopamine release were also investigated.

Materials and methods

Rats were unilaterally implanted with a guide cannula directed at the right nucleus accumbens (for procedures see Verheij and Cools 2007). The rats were allowed to recover from surgery for the next 7–10 days in dialysis cages. At 3 days prior to the start of the experiment, each rat was gently picked up (three times per day) in order to habituate to the procedure assessed on the day when accumbal dopamine was measured. At the start of the experiment, a dialysis probe was connected to a swivel and accumbal dialysates were analyzed for dopamine according to previously described procedures (see Verheij and Cools 2007). The probes had an in vitro recovery of 10–12% for dopamine (Verheij and Cools 2007). The dopamine sensitivity was 500 fg per sample (Verheij and Cools 2007). This sensitivity has repeatedly been shown to be sufficient for detecting the currently observed changes in the amount of dopamine (De Leonibus et al. 2006; Verheij and Cools 2007; Verheij et al. 2008).

As soon as the dopamine samples differed less than 10%, three baseline samples were taken and one group of rats was treated with 0.1 mM (2 µl/min for 40 min, intra-accumbens) of AMPT or its solvent (Ringer), whereas another group of rats was treated with 1 mg/kg (1 ml/kg, i.p.) of RES or its solvent (pH = 2.4). At 40 and 100 min after AMPT or its solvent and at 24 h after RES or its solvent, rats were subjected to a 40 min lasting intra-accumbens infusion of 0.01 mM (2 µl/min) of the alpha-1 adrenoceptor agonist PE.

The AMPT- and RES-induced changes of accumbal dopamine over time have already been published elsewhere (time effects of AMPT: Tuinstra and Cools 2000b; time effects of RES: Verheij and Cools 2007). The dopamine decreasing effects of these agents were found to be maximal and stable throughout the period that PE was given (see Tuinstra and Cools 2000b and Verheij and Cools 2007). Modified Ringer solution served as control for PE. At the end of the microdialysis experiments, rats were given an overdose of pentobarbital and were intracardially perfused with paraformaldehyde. Vibratome sections were cut to verify the location of the microdialysis probe.

It is important to realize that one can only measure a PE-induced increase of accumbal dopamine under the condition that the presynaptic pools of dopamine are not empty. For this reason, experiments were performed in high responders to novelty (HR) that were selected from the Nijmegen outbred strain of Wistar rats (Cools et al. 1990). It has previously been reported that an environmental or pharmacological challenge could still increase accumbal dopamine levels in these animals after the chosen treatment with AMPT (see Saigusa et al. 1999) or RES (see Verheij et al. 2008). HR were selected on the basis of their

locomotor response to a novel open field and defined as animals that travelled more than 6,000 cm in 30 min and habituated (no locomotor activity for a period of at least 90 s) after 840 s (Verheij and Cools 2007). All experiments were performed in accordance with institutional, national and international guidelines on animal care and welfare. Data were statistically analyzed using a two-way ANOVA with the factors treatment and time (for repeated measures). Post hoc *t* tests were performed where appropriate. All values are expressed as mean $\pm$ SEM.

Results

As much as 37% of the selected rats fulfilled the criteria for HR ($n = 61$). The average distance travelled on the open-field was 8.976 ± 261 cm in 30 min. The average habituation time of the animals was 1.384 ± 48 s. Representative placements of the dialysis probes are depicted in Fig. 1 (interaural level: 10.20 mm). Probes were found between interaural levels 10.2 and 11.2 mm (Paxinos and Watson 1986; Verheij and Cools 2007). Only data of rats with correctly placed probes were incorporated in the study ($n = 59$). Basal levels of dopamine were 3.8 ± 0.5 pg/20 min in HR treated with the solvent of AMPT (Ringer). The dose of 0.1 mM of AMPT reduced these levels of dopamine to $79 \pm 3.1\%$ at $t = 40$ min and to $81 \pm 5.9\%$ at $t = 100$ min (one sample *t* test, 40 min: $t_{(7)} = -6.840$, $P \leq 0.001$; 100 min: $t_{(7)} = -3.209$, $P = 0.015$; reductions similar to Tuinstra and Cools 2000b). The basal levels of dopamine were 2.9 ± 0.33 pg/20 min in HR treated with the solvent of RES. The basal concentration of dopamine did not differ

between rats that were treated with the solvent of AMPT or the solvent of RES (Student's *t* test: ns). The dose of 1 mg/kg of RES reduced the basal levels of dopamine to $56 \pm 8.3\%$ at 24 h (one sample *t* test, 24 h: $t_{(17)} = -5.277$, $P \leq 0.001$; reduction similar to Verheij and Cools 2007).

The dose of 0.01 mM of PE increased accumbal dopamine levels in rats treated with the solvent of AMPT (Fig. 2; one-way ANOVA, time effect: $F_{(7,56)} = 6.433$, $P \leq 0.001$) and in rats treated with the solvent of RES (Fig. 2; one-way ANOVA, time effect: $F_{(7,49)} = 9.521$, $P \leq 0.001$). The PE-induced increase of dopamine did not differ between the two groups of rats (Fig. 2; two-way ANOVA, treatment ($\times$ time) effect: ns). PE decreased dopamine levels in rats that were treated with AMPT 40 min earlier (Fig. 3a; two-way ANOVA, treatment $\times$ time effect: $F_{(5,70)} = 3.688$, $P = 0.005$) and increased dopamine levels in rats that were treated with AMPT 100 min earlier (Fig. 3b; two-way ANOVA, treatment $\times$ time effect: $F_{(5,70)} = 10.496$, $P \leq 0.001$). The PE-induced dopamine increase in the latter group of AMPT-treated rats was equal to the PE-induced dopamine increase that was observed in the control rats treated with the solvent of AMPT (Fig. 3b versus Fig. 2; two-way ANOVA, treatment ($\times$ time) effect: ns). PE increased dopamine levels in rats that were treated with RES 24 h earlier (Fig. 4; two-way ANOVA, treatment $\times$ time effect: $F_{(5,80)} = 8.964$, $P \leq 0.001$). The PE-induced dopamine increase in these RES-treated rats was equal to the PE-induced dopamine increase that was observed in the control rats treated with the solvent of RES (Fig. 4 versus Fig. 2; two-way ANOVA, treatment ($\times$ time) effect: ns).

Fig. 1 Three unilateral microdialysis probe tracks located in the right nucleus accumbens (see also Verheij and Cools 2007). The probe protrudes 2 mm below the distal end of the guide cannula. The brain region in which correctly placed probes were found is indicated in gray. IA corresponds to the distance (mm) from the interaural line according to Paxinos and Watson (1986). NAC nucleus accumbens, CPU caudate putamen, CC corpus callosum

Fig. 2 Effects of intra-accumbens infusion of 0.01 mM of the alpha-adrenoceptor agonist phenylephrine in rats treated with the solvent of either alpha-methyl-para-tyrosine (filled symbols) or reserpine (open symbols). Phenylephrine increased accumbal dopamine levels in these control rats. The black line represents the infusion time of phenylephrine (40 min). *Significant increase relative to the baseline (one sample *t* tests)

Fig. 3 **a** Effects of intra-accumbens infusion of 0.01 mM of the alpha-adrenoceptor agonist phenylephrine at 40 min after 0.1 mM of alpha-methyl-para-tyrosine. Phenylephrine decreased accumbal dopamine levels 40 min after alpha-methyl-para-tyrosine. The *black line* represents the infusion time of phenylephrine (40 min). *Significant decrease compared to control (Student's *t* tests). **b** Effects of intra-accumbens infusion of 0.01 mM of the alpha-adrenoceptor agonist phenylephrine at 100 min after 0.1 mM of alpha-methyl-para-tyrosine. Phenylephrine increased accumbal dopamine levels 100 min after alpha-methyl-para-tyrosine. The *black line* represents the infusion time of phenylephrine (40 min). *Significant increase compared to control (Student's *t* tests)

Discussion

The AMPT-induced changes in the baseline levels of accumbal dopamine at 40 and 100 min after its administration are very similar to our previously reported AMPT-induced changes in accumbal dopamine (Tuinstra and Cools 2000b). The same holds true for the RES-induced changes in the baseline levels of accumbal dopamine at 24 h after its administration (Verheij and Cools 2007). Our previous studies have shown no signs of an increased synthesis of dopamine at 40 min after AMPT or at 24 h after RES.

Fig. 4 Effects of intra-accumbens infusion of 0.01 mM of the alpha-adrenoceptor agonist phenylephrine at 24 h after 1 mg/kg of reserpine. Phenylephrine increased accumbal dopamine levels 24 h after reserpine. The *black line* represents the infusion time of phenylephrine (40 min). *Significant increase compared to control (Student's *t* tests)

The alpha-1 adrenoceptor agonist PE (Ruffolo and Hieble 1994) strongly increased accumbal dopamine levels in control rats (Fig. 2), confirming the outcome of our previous studies that PE acts at presynaptic alpha-adrenoceptors in the nucleus accumbens of otherwise untreated rats (Tuinstra and Cools 2000a; Cools and Tuinstra 2003; Aono et al. 2007). In contrast, PE decreased accumbal dopamine levels in rats that were treated with AMPT 40 min earlier (Fig. 3a). The possibility that PE did not increase dopamine release because the AMPT-sensitive dopamine pools of these rats were empty can be rejected since alpha-adrenoceptors do not control the release of dopamine from this type of pool (Tuinstra and Cools 2000b; see also Verheij and Cools 2008). The present finding that PE reduced dopamine levels in HR treated with AMPT, therefore, demonstrates that this agonist stimulates postsynaptic alpha-adrenoceptors in these rats. This finding is in line with the fact that stimulation of accumbal postsynaptic alpha-adrenoceptors inhibits the release of dopamine from RES-sensitive pools (see "Introduction"). Furthermore, these data confirm our hypothesis that AMPT increases the sensitivity of accumbal postsynaptic alpha-adrenoceptors (see "Introduction"). The present study shows that noradrenaline that regulates the dopamine derived from RES-sensitive vesicles is derived from AMPT-sensitive pools. The finding that the PE-induced decrease of dopamine seen in rats treated 40 min earlier with AMPT (Fig. 3a) was replaced by a PE-induced increase of dopamine in rats treated 100 min earlier with AMPT (Fig. 3b) illustrates that the ability of AMPT to change the state of the alpha-adrenoceptors in the nucleus accumbens was time-dependent and reversible.

RES did not affect the ability of PE to increase the amount of accumbal dopamine (Fig. 4). In fact, the PE-induced dopamine increase in the RES-treated rats was identical to the PE-induced dopamine increase that was observed in the control rats treated with the solvent of RES (Fig. 4 versus Fig. 2). These data demonstrate that PE acted at presynaptic alpha-adrenoceptors in these rats and that RES did not change the state of postsynaptic alpha-adrenoceptors. Previous studies have provided evidence that alpha-adrenoceptors control the release of dopamine from RES-sensitive dopamine pools (Cools and Verheij 2002; see also Verheij and Cools 2008). The present finding that PE still increased dopamine in RES-treated HR can be ascribed to the fact that the applied dose of RES did not completely empty the dopaminergic storage vesicles in this type of rat (see Verheij et al. 2008). One could argue that the dose of 1 mg/kg of RES was too low to result in more sensitive postsynaptic adrenoceptors. This explanation is quite unlikely because the applied dose of 1 mg/kg of RES strongly increased the sensitivity of the postsynaptic beta-adrenoceptors in the nucleus accumbens of HR (Verheij and Cools submitted). The increase of the sensitivity of these beta-adrenoceptors can be explained by the well-known action of RES to decrease accumbal noradrenaline levels (Pan et al. 1993). The notion that the noradrenaline that acts at accumbal alpha-adrenoceptors is not influenced by RES (Fig. 4), whereas the noradrenaline that acts at accumbal beta-adrenoceptors is affected by this drug (Verheij and Cools submitted) demonstrates that RES-induced changes in the overall amount of accumbal noradrenaline do not reflect the processes that actually take place at each distinct type of accumbal adrenoceptor. Measuring adrenoceptor-specific changes in accumbal dopamine have previously been found to be a valid and reliable method for reaching conclusions about the noradrenergic activity at the level of one single type of accumbal adrenoceptor (Tuinstra and Cools 2000a). It is evident that for the present study, measuring adrenoceptor-specific changes in accumbal dopamine levels is preferred above measuring changes in the total amount of accumbal noradrenaline. On the basis of the results obtained by this method, we hypothesize that the pools that contribute to the release of noradrenaline at postsynaptic alpha-adrenoceptors of the nucleus accumbens are relatively insensitive to RES. The concept of a RES-resistant compartment of noradrenaline has also been suggested by others (Kopin 1964; Van Orden et al. 1970; Enna and Shore 1974; Schwab and Thoenen 1983; Yamazaki et al. 1997). Our data suggest that the compartment that releases noradrenaline at postsynaptic alpha-adrenoceptors in the nucleus accumbens contains AMPT-sensitive and newly synthesized neurotransmitter that is not accumulated in RES-sensitive vesicles. It remains to be investigated whether this

noradrenergic compartment consists of RES-resistant cytoplasmatic pools or RES-insensitive vesicles.

The data provide direct evidence for the previously reported hypothesis that AMPT can directly (by inhibiting dopamine synthesis) and indirectly (by inhibiting noradrenaline synthesis) change accumbal dopamine levels (Saigusa et al. 1999). The present findings reveal that compounds that directly or indirectly interact with accumbal alpha-adrenergic mechanisms should be considered as agents that can have important therapeutic effects in patients suffering from diseases in which accumbal dopamine is known to be involved. In this respect, it is important to mention that alpha-adrenergic agents have indeed been found to exert therapeutic effects in animal models of Parkinson's disease (Haapalinna et al. 2003) and addiction (Erb et al. 2000). Moreover, noradrenergic agents may also be used to treat patients with attention deficit hyperactivity disorder, schizophrenia and depression (Zhou 2004; Buitelaar et al. 2007). This aspect is elaborated in detail elsewhere (Aono et al. 2007; Ikeda et al. 2007; for review see Verheij and Cools 2008).

Finally, it is important to realize that the direct and indirect therapeutic effects of noradrenergic agents strongly depend on the amount of endogenous noradrenaline in the synapse. In fact, the present study indicates that a noradrenergic agonist may have postsynaptic effects in individuals with low levels of endogenous noradrenaline, whereas the same agonist may have presynaptic effects in individuals with high levels of this neurotransmitter.

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