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Developmentally induced imbalance of dopaminergic fibre densities in limbic brain regions of gerbils (*Meriones unguiculatus*)

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Summary. It is well established that epigenetic factors influence the maturation of neurotransmitter systems. Social isolation as well as an early intervention with methamphetamine (MA) lead to a diminished maturation of dopaminergic (DA) fibres in cortical and striatal areas in the brain of Mongolian gerbils. The aim of this study was to prove whether isolated rearing (IR) and the application of a single dose of MA on postnatal day 14 affect the maturation of DA fibres in caudal limbic areas. Therefore the DA fibre densities were quantified in the dorsolateral and ventrolateral entorhinal cortex (EC), the ventral subiculum (SUB) and in three amygdala nuclei – the basolateral (BLA), the lateral (LA) and the central (CA) nucleus. Our results showed that IR and an early MA application led to an increase of DA fibre densities in various caudal limbic areas. Whereas the BLA was affected by both IR and MA, the LA and the medial left CA were only influenced by MA in IR animals. The DA fibre surplus in the ventrolateral EC was significant in MA treated ER and IR animals in the left and right hemisphere, respectively. The SUB and the dorsolateral EC remained unaffected by both epigenetic factors. Altogether, the BLA seems to be the area which responds most sensitively to IR and MA. Previous studies in our laboratory showed a suppressive maturation of DA fibres in the prefrontal cortex (PFC) and nucleus accumbens (NAC) induced by the same set of epigenetic factors. Thus, due to the close functional connection between the PFC and limbic areas, it could be assumed that the suppressive maturation of prefrontal DA fibres implicates an enhancement of DA innervation densities in caudal limbic areas. Imbalances in the morphology and physiology of the different DA projections are suggested here to be crucial in the aetiology of schizophrenia.

Keywords: Dopamine, caudal limbic areas, fibre overshoot.

Introduction

There is increasing evidence that the regulation of corticolimbic functions by the neurotransmitter dopamine (DA) is essential for psychobiological adaptation in development. Psychotic disorders appear to be at least partly due to a complex imbalance within the DA system. Human studies have shown that low DA activity in the cortex coincides with high activity in subcortical limbic regions of schizophrenic patients (revs. Davis et al., 1991; Jentsch et al., 2000; Sesack and Carr, 2002; Meyer-Lindenberg et al., 2002). These observations are consistent with others coming from animal lesion and pharmacological studies which suggest that hypodopaminergic activities of the prefrontal cortex (PFC) may lead to hyperdopaminergic transmissions in the dorsal and ventral striatum and this inverse activity pattern probably induces behavioural impairment (rev. Nieoullon, 2002). Obviously, DA transmission in the mesocortical, mesostriatal and mesolimbic projections is controlled in a complex and interdependent way, which has important implications for the enormous spectrum of psychotic disorders (rev. Le Moal and Simon, 1991). However, the regional characteristics of DA maladaptations producing psychiatric disorders are by no means understood. Experimental interventions manipulating the postnatal DA maturation can offer valuable insights.

Dopaminergic fibres of the mesocorticolimbic projection originate in a rather small midbrain area, the VTA (Fallon et al., 1978; Swanson, 1982), but discretely target multiple subregions of the dispersely organised corticolimbic circuitry (Björklund and Lindvall, 1984; Descarries et al., 1987; Yoshida et al., 1988). Remarkably, each DA projection field is characterised by its own time sequence pattern of maturation in postnatal life. Principally, the maturation of the mesocorticolimbic DA projection progresses from caudal to rostral areas. In rodents and primates, the DA fibre densities of caudal limbic areas, namely the hippocampus (HC), the amygdala and the entorhinal cortex (EC), peak early in development and decline slightly before acquiring the adult pattern (Verney et al., 1985; Erickson et al., 1998). In the nucleus accumbens (NAC) of rats the number of varicosities of DA fibres increases strongly from postnatal day (PD) 8 to PD 20 and the adult DA innervation pattern is reached on PD 28 (Voorn et al., 1988). For the rat's dorsal and ventral striatum it was shown that the DA-transporter densities increase till puberty (Tarazi et al., 1998; Moll et al., 2000) and decrease steadily in further development (Moll et al., 2000). In contrast, the DA fibres of the orbital PFC still mature up to sexual maturity and portions of the medial PFC innervation obtain adult patterns at young adulthood (Kalsbeek et al., 1988; Dawirs et al., 1993). Therefore, developmentally induced maladaptation during transmitter maturation may become effective in quite different stages in the various targets of DA fibres.

In the concerted action of neuronal networks the maturation of transmitters is activity-dependent. Environmental and/or pharmacologically induced interventions in postnatal life lead to longlasting alterations of transmitter functions (revs. White et al., 1996; Hall, 1998; Lapiz et al., 2003; Steketee, 2003). Therefore, individual portions of the mesocorticolimbic DA projection may be susceptible to different disturbances during selective stages of postnatal maturation. Two

experimental challenges have been intensively investigated: First, isolated rearing (IR) compared with enriched rearing (ER) has been shown to interfere with the anatomical maturation (Winterfeld et al., 1998; Neddens et al., 2001; Lehmann et al., 2002) and function (Jones et al., 1992; Heidbreder et al., 2000) of DA in prefrontal, striatal and amygdaloid regions. Second, the application of a single dose of methamphetamine (MA) on PD 14, which we know to induce acute and selective autotoxic effects on the DA targets in the maturing PFC of gerbils (Teuchert-Noodt and Dawirs, 1991) also affects the DA innervation in the adult PFC (Dawirs et al., 1994) and NAC (Neddens et al., 2002). In all rostral brain areas where DA fibre densities were studied, a decline of DA fibres was detected in IR and MA treated animals (Dawirs et al., 1994; Winterfeld et al., 1998; Neddens et al., 2001, 2002; Lehmann et al., 2002).

The aim of the present study was to complement former studies and investigate further adaptive changes of the DA balance within the corticolimbic system. Since the immunohistochemical approach permits us to quantify the DA fibre densities in multiple brain regions simultaneously, we made use of the same set of afore mentioned interventions and focussed on DA innervation patterns in limbic terminal fields. We quantified the DA fibre densities in young adult gerbils (PD 90) in the dorso- and ventrolateral EC, the three DA innervated nuclei of the amygdala, which are the basolateral (BLA), central (CA) and lateral (LA) nucleus, and in the ventral subiculum (SUB) with software for image analysis.

Material and methods

Animals and rearing conditions

All experimental procedures were approved by the appropriate committee for animal care in accordance with the European Communities Council. For this study 34 male gerbils were used. Sixteen of them were bred in standard makrolon cages (type IV) under impoverished condition while 18 of them were bred in semi-naturally structured compounds (1×1 m; enriched condition). At weaning (30 days), the gerbils that were born in cages were assigned to impoverished conditions (IR, animals kept alone in standard makrolon cages type III), while the other group grew up under enriched rearing conditions (ER, kept as a group of siblings in semi-naturally structured compounds containing branches and hiding opportunities), both for further 60 days. On PD14 a total of sixteen pups received a single injection of methamphetamine hydrochloride (50 mg/kg; i.p.), nine gerbils of the ER group and seven gerbils of the IR group. The remaining eighteen gerbils, nine of either rearing group, were sham-treated by a single injection of saline. Under all sets of conditions food and water were provided *ad libitum*. All gerbils were kept on natural day/night cycles during summer season.

Immunohistochemistry

Preparation of tissue: Animals were transcardically perfused under deep chloralhydrate anaesthesia (1.7 g/kg, i.p.). The perfusion was performed with 60 ml cold 0.05 M phosphate buffer (pH 6.2), containing 1% sodium metabisulfite, followed by 500 ml 5% glutaraldehyde with 1% sodium metabisulfite in 0.1 M phosphate buffer (pH 7.5), and finally by wash buffer containing 0.05 M tris buffered saline (TBS) with 1% sodium metabisulfite (pH 7.5). Immediately after perfusion, the brains were dissected and 50 µm thick frontal sections cut with a vibratome (Leica VT 1000 S, Nussloch, Germany) and subsequently collected in wash buffer at 4°C.

General procedure: The first steps of the protocol were also performed in wash buffer with gentle agitation of the slices. The immunohistochemical procedure used (1) a 30 min preincubation in 10% normal goat serum and 0.4% Triton X100, (2) rabbit anti-dopamine serum (DiaSorin,

Stillwater, MN) diluted 1:600 with 1% normal goat serum and 0.4% Triton X100 for 40 h. The next steps were performed in 0.05 M Tris-HCl (pH 7.5) and were each followed by a 30 min washing in Tris-HCl. (3) A 30 min incubation in biotinylated goat anti-rabbit serum (Sigma) diluted 1:20 with 1% normal goat serum, (4) ExtrAvidin-Peroxidase (Sigma) diluted 1:20 for 30 min. (5) The staining solution contained 0.05% 3,3′-diaminobenzidine with 0.01% H_2O_2. After 4 min of staining, the sections were washed, mounted on glass slides, dried at room temperature

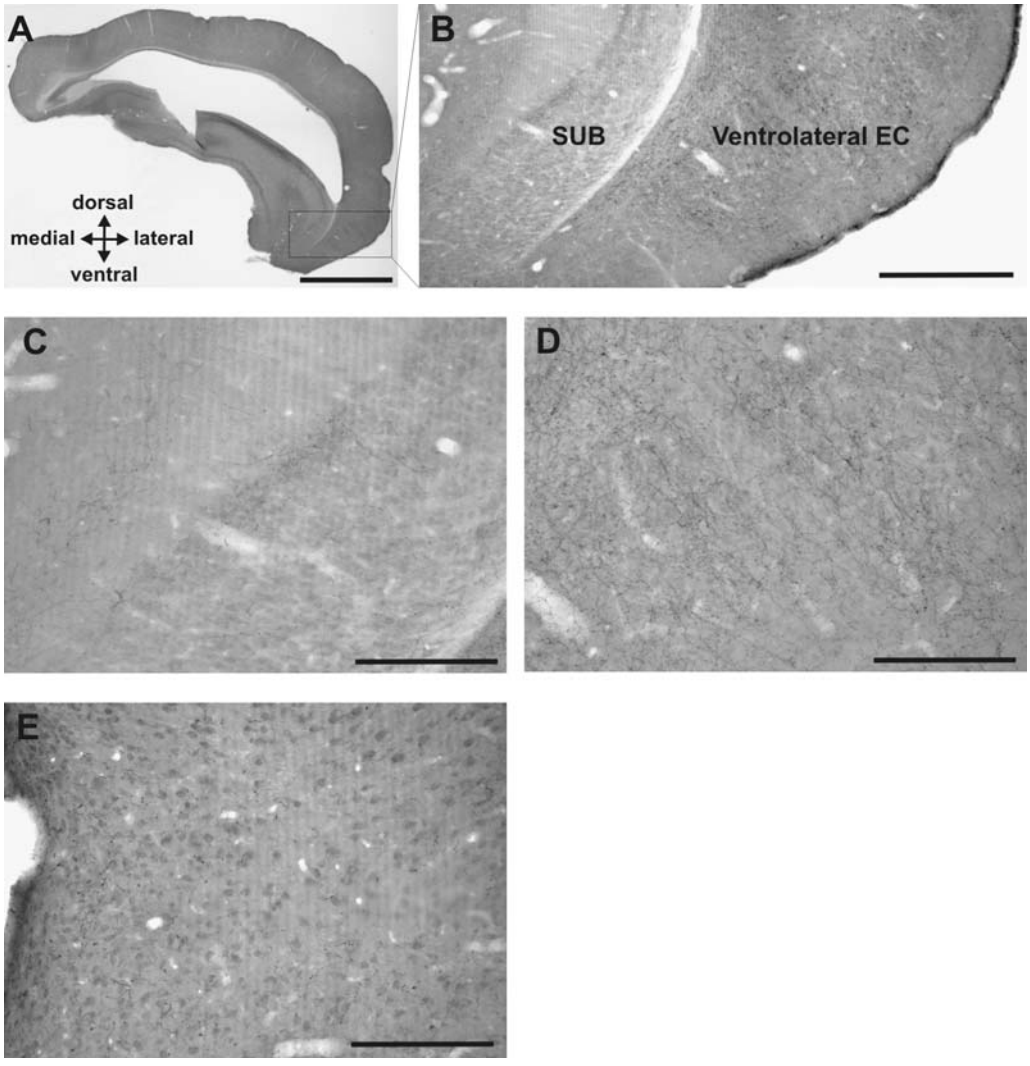

Fig. 1. A Brightfield photomicrograph of a representative coronar section at the level of the entorhinal cortex (EC). The area of the rectangle is magnified in (**B**) and comprises the ventral subiculum (SUB) and the ventrolateral EC. Within the cellular layer of the SUB DA fibres are only found in a restricted area at the border to the CA1 region of the hippocampus. In the molecular layer of the SUB the fibres run tangentially to the cellular layer (**C**). The DA fibres of the ventrolateral EC are arranged in clusters (**D**) and show rostrally a dense fibre network which thins out to caudal levels. On the other hand the dorsolateral EC, which is located dorsally to the ventrolateral EC, is less DAergic innervated and DA fibres appear densest in the deeper layers (L III–VI). In the superficial layers DA fibres are only found sporadically (**E**). Scale bars: 2 mm (**A**), 500 μm (**B**) and 200 μm (**C–E**)

overnight, dehydrated, mounted in DePeX and coverslipped. Control sections were treated by the same procedure but omitting the rabbit-anti-dopamine serum and showed no specific staining.

Quantification of DA innervation

The brain was serially cut across the entire rostro-caudal extent of the amygdala and the EC. For quantification every other slice of the right and left hemisphere was used. In the EC, the ventral SUB (Fig. 1) and the amygdala (Fig. 2) different test fields were defined. The measurements in

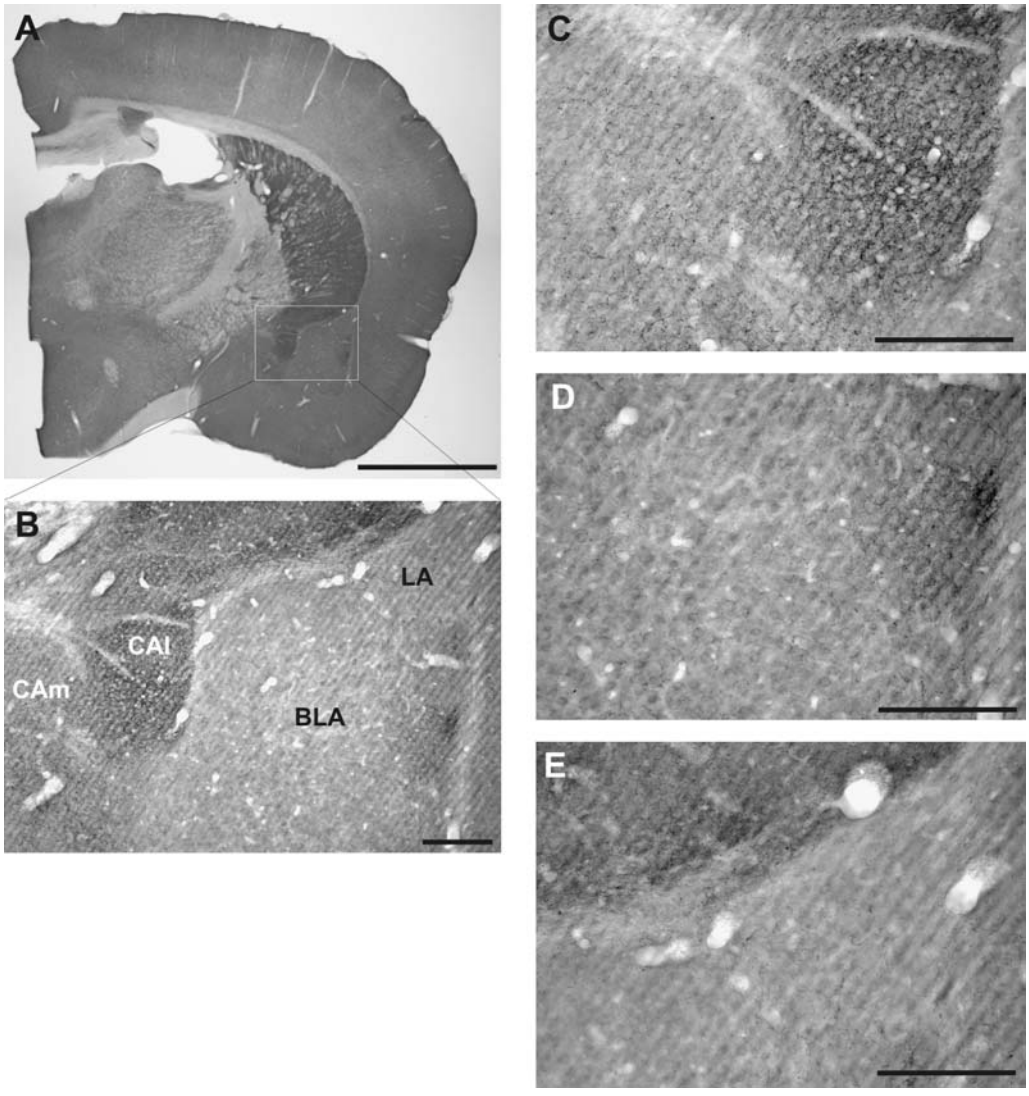

Fig. 2. Brightfield photomicrograph of a representative coronar section at the level of the amygdala (**A**). The rectangle shows the analysed amygdaloid nuclei, which are highlighted in (**B**). The DA innervation patterns of the amygdaloid nuclei are generally different. The lateral part of the central nucleus (CAl) is densely innervated by DA fibres whereas the medial part of this nucleus (CAm) is rather moderately innervated (**C**). The basolateral nucleus (BLA; **D**) shows a sparse DAergic innervation, which is densest in its lateral part near the capsula externa. (**E**) The lowest fibre density appears in the lateral nucleus (LA). Scale bars: 2 mm (**A**) and 200 μm (**B**–**E**)

the EC comprised the dorsolateral (layers III–VI) and ventrolateral part, which correspond to the DLEA and VLEA, respectively, defined by Krettek and Price (1977). The testfields in the SUB laid in the ventral part at the border to the CA1 area. The molecular layer (SUBml) and cellular layer (SUBcl) were separately analysed. Images were taken at 125-fold magnification of 8 consecutive slices. For the central amygdaloid nucleus (CA) images were taken of its medial (CAm) and lateral (CAl) part in 6 consecutive slices at 400-fold magnification with oil immersion. In the basolateral nucleus (BLA) two testfields were placed and images were taken in 7 consecutive slices at 200-fold magnification. For each image all detectable DA fibre fragments were visualised by the use of a brightfield microscope (Polyvar, Reichert-Jung, Vienna, Austria) and a digital camera for microscopy (ProgRes 3008, Jenoptik, Jena, Germany). The fibres were detected using the valleys function, which depicts the grey value difference of adjacent pixels and transform the result into a binary image (KS300, Jenoptik, Jena, Germany). The DA fibre densities were calculated as the percentage area of the fibres within each testfield.

Data analysis

For the comparison mean values were calculated from the single testfield data over the rostro-caudal extent of the respective brain area for each animal. Mean values for each animal group were computed as arithmetic means $\pm$ standard deviation (S.D.) and compared by t-test (two-tailed) with preceding F-test. Region- and group-specific effects were additionally tested by a three-way multivariate analysis of variance (MANOVA) computed with Statistica 6 (StatSoft, Tulsa, USA). The levels of significance were set at $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***).

Results

The DA innervation pattern in gerbils' amygdala and caudal limbic areas is similar to that described for the rat (Freedman and Cassell, 1994; Asan, 1998; Gasbarri et al., 1997). In the amygdala the lateral part of the CA shows the densest DA fibre network (Fig. 2C), the medial CA (Fig. 2C) and the ventrolateral EC (Fig. 1D) have moderate to high fibre densities, moderate fibre densities are found in the BLA (Fig. 2D), the dorsolateral EC (Fig. 1E) and ventral subiculum (Fig. 1C) and the lowest fibre density appears in the LA (Fig. 2E). The fibre density of the ventrolateral EC thins out from rostral to caudal and at more caudal levels the DA fibres are arranged in several clusters (Fig. 1D). In the dorsolateral EC DA fibres are mainly visible in the deeper layers (III–VI; Fig. 1E). The ventral subiculum shows a striking dopaminergic innervation pattern because within the cellular layer only a narrow stripe at the border to CA1 is innervated by DA fibres (Fig. 1C). In the molecular layer the fibres run tangentially and have their highest density even at this narrow stripe.

Influence of rearing conditions

The BLA is the only analysed structure which is significantly affected by rearing conditions. Impoverished reared animals show an increase of DA fibre densities in the BLA of 17% and 23% in the left and right hemisphere, respectively (Fig. 3C–D).

Influence of methamphetamine

In principle the MA treatment of animals leads to an increase of DA fibre densities in various caudal limbic areas. Its effect is generally more pronounced in IR than in

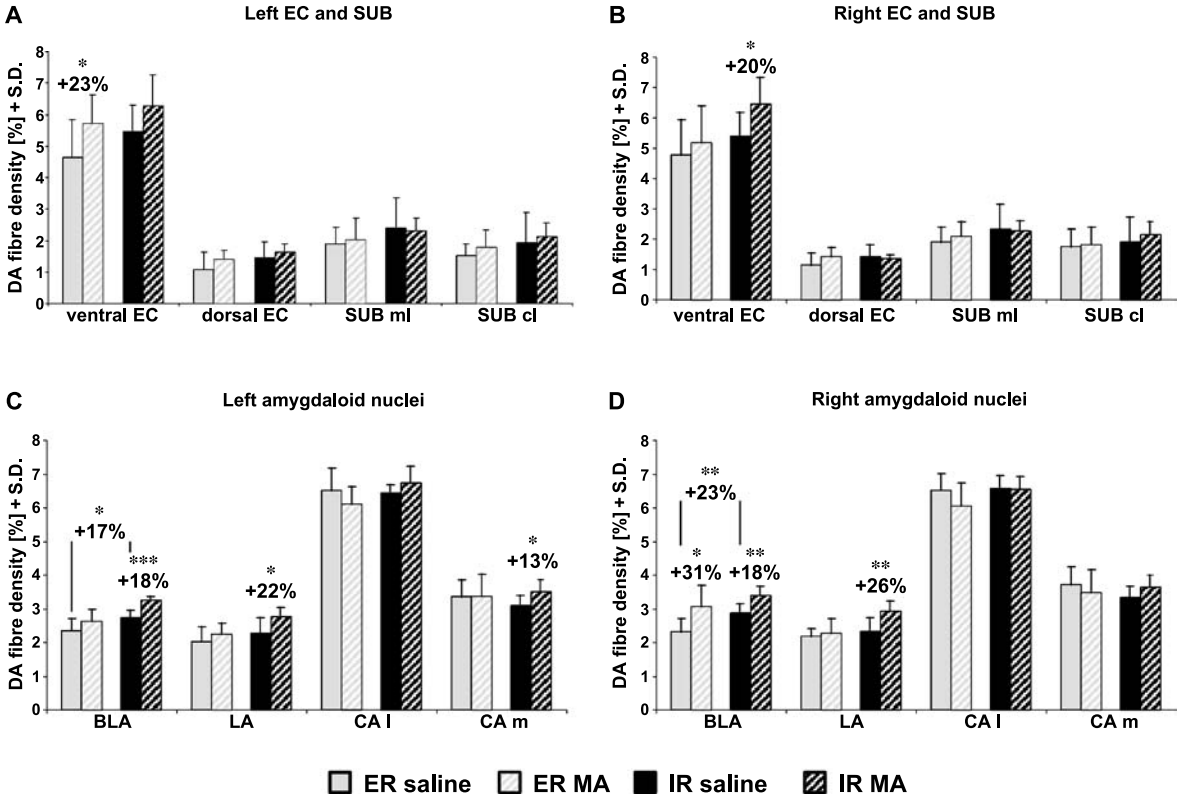

Fig. 3. Dopamine (DA) fibre densities in the analysed areas of gerbils from enriched (ER) and impoverished rearing (IR) conditions treated with either methamphetamine (MA) or saline given by means ± standard deviation (S.D.). **A**, **B** show the results of the left and right hemisphere, respectively of the entorhinal cortex (EC) and the subiculum (SUB). The DA fibre densities in the different amygdaloid nuclei, basolateral (BLA), lateral (LA) and central (CA), of the left and right hemisphere are given in (**C**, **D**), respectively. $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***)

ER animals (MANOVA: ER: saline vs. MA, $F = 5.6955$, $p = 0.0174^{*}$; IR: saline vs. MA, $F = 19.9829$, $p < 0.0001^{***}$). Methamphetamine treatment of IR animals leads to a fibre overshoot of 20% in the ventrolateral EC of the right hemisphere. In the amygdala a fibre surplus of 18% in the BLA of each hemisphere and of 22% and 26% in the LA of the left and right hemisphere, respectively, is detected. The CAm shows an overshoot of DA fibres of 13% in the left hemisphere (Fig. 3A–D). The MA application of ER animals increases the DA fibre densities of 23% in the ventrolateral EC of the left hemisphere and of 31% in the BLA of the right hemisphere (Fig. 3A, D). The dorsolateral EC, the SUB and the lateral part of the CA remain unaffected by both epigenetic factors (Fig. 3A–D).

Although the results revealed some hemisphere-specific experimental effects, no significant asymmetry of the DA fibre density could be detected (MANOVA: $F = 0.8721$; $p = 0.3509$).

Discussion

Evaluations of DA fibre densities in the present study have shown that both interventions, IR conditions and the postnatal MA treatment, do exert region-

specific effects in distinct limbic areas. In the densely aggregated DA clusters of the ventrolateral EC, the early MA application enhances the DA fibre densities in both ER (left hemisphere) and IR animals (right hemisphere). In contrast, the less innervated dorsolateral EC and SUB remain unaffected by any treatment. In the amygdala the MA challenge in IR animals leads to an enhancement of DA fibres in the LA and CAm. The DA fibre density of the BLA is affected by both experimental variables, which suggests this nucleus to be the most susceptible amygdaloid structure. Remarkably, the lateral CA, which is completely filled by DA terminations, shows no adaptive changes at all. Thus, the susceptibility of DA fibres is not correlated to the absolute fibre density of the area concerned. On the whole, IR animals reacted more sensitively to the early MA treatment as compared to ER animals.

The presented data on a DA fibre surplus in the EC and BLA, including recent ones that concern suppressive DA fibre maturation in the PFC, NAC and caudatus-putamen of this animal model (Dawirs et al., 1994; Winterfeld et al., 1998; Neddens et al., 2001, 2002; Lehmann et al., 2002), show that the DA fibre maturation of the different parts of the mesocorticolimbic system could be influenced in an inverse manner by epigenetic factors. Our suggestion is that the main subdivisions of the mesocorticolimbic DA projection, the mesocortical, the mesostriatal and mesolimbic one, closely interact in function and dysfunction and presumably interact in a hierarchical fashion. Using invasive 6-hydroxydopamine intoxication it has been demonstrated in adult rats that the pharmacologically lesioned PFC affects the DA turnover in NAC particularly under stress (Pycock et al., 1980; Martin-Iversen et al., 1986; Deutch et al., 1990; Rosin et al., 1992; King et al., 1997). The authors independently suggested that the activity efflux from the PFC to the ventral striatum generally influences the DA activity in this subordinated area. This idea is affirmed by our studies of DA fibre maturation of the NAC. The MA treatment at PD14 produced significant deficits of DA fibre densities up to adulthood in the core of IR gerbils and in both core and shell of the ER group (Neddens et al., 2002). The authors argued that presumably the MA intervention affected the mesostriatal DA projection just during a most critical period of maturation. Although it is well known that monoamine systems of rats are affected by a single high dose of MA due to the production of neurotoxic 6-hydroxydopamine and several other physiological mechanisms (rev. Seiden and Sabol, 1996; Seiden and Vosmer, 1984; Fukumura et al., 1998), it has been demonstrated that in gerbils the MA intoxication on PD14 selectively damaged prefrontal axon terminals (Teuchert-Noodt and Dawirs, 1991) and led to a suppressive maturation of prefrontal DA fibres up to adulthood (Dawirs et al., 1994). Therefore, a maladaptation of DA fibre densities in the NAC may be brought about by the weakened control coming from an underdeveloping PFC.

Le Moal and Simon (1991) proposed that the DA regulation in the anatomical and functional interdependent mesocorticolimbic circuitry might be ‘‘organised in a hierarchial manner, with the PFC acting as the highest instance’’. Thus, the PFC might be in a position to control, strengthen or weaken and even disturb the function not only of the corticostriatal but even of the whole limbic circuitry. For instance, Rosenkranz and colleagues could

demonstrate that the output neurons of the BLA are under the regulatory control of prefrontal efferents which are presynaptically modulated by DA (Rosenkranz and Grace, 2001, 2002; Grace and Rosenkranz, 2002). Thus, the PFC could exert its main influence on the activity of far distant mesolimbic areas by direct projections to the limbic termination fields. Within the amygdala complex the PFC has strong reciprocal connections particularly to the BLA and to a lesser extent to the LA (McDonald et al., 1996; Pitkanen, 2000). Mediated by distinct projections of the BLA, the ventrolateral EC and the CAm participate in the PFC activity flow (Krettek and Price, 1977, 1978; Pikkaraninen et al., 1999). Based on the paradigm that processes of maturation are activity-dependent, the DA fibre maturation should be dependent on extrinsic and intrinsic activities and presumably particularly on the activity of the prefrontal efferents to the termination fields. Likewise the PFC could indirectly affect DA maturation of caudal limbic structures via reciprocal connection to the VTA (Sesack and Pickel, 1992; rev. Kalivas, 1993). However, the prefrontal influence via the VTA seems not very likely to us, since the VTA can be regarded as an anatomical and functional continuum and DA neurons are equipped with intense compensatory mechanisms (rev. Le Moal and Simon, 1991). Moreover, there is no proof that prefrontal projections to the VTA generally terminate on DA neurons which project to the amygdala and entorhinal cortex. Therefore, our interpretation for the results would be that malfunctional efferents from the PFC, which are impaired by the suppressive prefrontal DA maturation (Dawirs et al., 1994; Winterfeld et al., 1998; Neddens et al., 2001), may cause selective maladaptations of DA fibre densities in specific limbic target areas. This interpretation is supported by the result that alterations of DA innervation were found in those brain regions which are closely interconnected with the PFC. Thus, selective effects on the limbic DA target fields support the idea of correspondingly selective dependences on intrinsic and/or extrinsic activities which function in an interdependent manner and modulate large regions of the brain. In other words, the ventrolateral EC, the BLA, the LA and the medial part of the CA are crucial points in respect of vulnerability of DA fibre maturation of the mesocorticolimbic system, whereas other amygdaloid and entorhinal areas seem to be less influenced by these intrinsic activity disturbances.

There are two versions of how the enhancement of DA fibres in caudal limbic areas may adjust to suppressive ones in the prefrontal cortex. First, following the pruning paradigm, the disconnection of mesocortical from mesolimbic DA projections in early postnatal life may produce a fibre overshoot sprouting nearby the VTA, i.e. in limbic areas. This mechanism has been demonstrated by systemic neurotoxic lesions of serotonergic and noradrenergic pathways of neonatal rats, which produced subsequent hyperinnervations in areas proximal to the brainstem nuclei, and hypoinnervations in distal aminergic target fields (Jonsson and Hallman, 1982; Fischer et al., 1995). Other literature reports that a partial lesion of the medial PFC of rat pups induced the mesocortical DA projection to evade into unlesioned frontal cortical fields (de Brabander et al., 1991, 1992). Furthermore, lesion-induced regenerative DA fibre sprouting has been proven for the mesostriatal DA projection (Mitsumoto et al., 1998; Bezard et al., 2000). However, no pathologically induced sprouting

effects have yet been shown for DA projections into caudal limbic areas. In primates and rats the normal process of DA maturation is characterised by a transient early postnatal fibre surplus in caudal limbic target fields (Verney et al., 1985; Erickson et al., 1998). The following decline of DA fibres continues into adolescence. Remarkably, this regressive process is correlated with the prolonged DA fibre maturation in the PFC (Kalsbeek et al., 1988; Dawirs et al., 1993). Therefore, the second possible version might be that the normal decline of the transient DA fibre surplus in limbic areas is suppressed by the epigenetically induced disconnection from the prefrontal activity control.

The present study displays the BLA as the most sensitive caudal limbic structure affected by the developmentally induced disturbances. This observation gets support from recent comparable investigations showing that the serotonergic innervation pattern of the BLA is also severely affected by the same set of interventions (Lehmann et al., 2003). Of all areas investigated in this study, the BLA has the strongest reciprocal connection with the PFC (Pitkanen, 2000). The late maturation of this connectivity has recently been shown and was proposed to influence the development and integration of normal or abnormal emotional behaviour during adolescence (Cunningham et al., 2002). These findings may help to explain why an apparently moderate chronic disturbance during development, namely IR condition, is sufficient to selectively affect the monoaminergic maturation of the BLA. On the other hand the early single MA intoxication represents an acute severe impairment in a critical period of DA maturation. In combination with social deprivation the single application is apparently sufficient to strongly disturb the balance of the mesocorticolimbic system. As a consequence not only the BLA is affected but also other interconnected caudal limbic areas. Thus, the effect of the MA intoxication seems to depend on the complexity of the social environment. This result strongly demands to think about postnatally acquired individual predispositions in view of clinical psychopharmacology.

On the whole, we come to the conclusion that during postnatal development the mesocorticolimbic DA projection forms an integrated whole, in which the role of retarded PFC maturation patterns might be to strike the right balance for cortical and limbic integrative functions. Consequently, the disturbance of this balance in early childhood may lead into another balance, which is a pathological one. The coincidence of two severe non-invasive interventions has shown that a pathological imbalance can produce multiple features of psychiatric diseases in dependence on individual predisposition.

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