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Prenatal cocaine exposure: effects on locomotor activity in rat offspring

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Abstract

This study examines the developmental effects of prenatal exposure to cocaine in the rat, evaluated during the first month of life through open-field behavior. The offspring of Wistar dams that received 60 mg/kg of cocaine, from gestational day 8 to 22, were examined in the open-field during the second, third and fourth weeks of postnatal life in three consecutive 15-min daily sessions, starting on postnatal day (PND) 14, (PND 14–16), PND 21 (PND 21–23) and PND 28 (PND 28–30). Results show that prenatal exposure to cocaine increased total activity and rearing behavior on PND 22 and PND 29. Also, on PND 14, cocaine-exposed animals reared significantly more than control rats. There were no significant differences in the frequency of center and peripheral ambulation, nor in the defecation rate. The present results evidence alterations in the emotional behavior of rats prenatally exposed to cocaine. The delayed onset of exploration in the open-field observed in cocaine-exposed animals suggests that they take more time to become habituated to a novel and open environment.

Keywords: Open-field behavior; Development; Cocaine; Prenatal; Rat

1. Introduction

Prenatal exposure to cocaine can produce several deleterious outcomes on the neurobehavioral development of the offspring (Church and Overbeck, 1990; Spear, 1996). However, there are some discrepancies in literature about the potential effects of cocaine administration during pregnancy. While some studies have observed no signs of toxicity following prenatal cocaine exposure (Fantel and MacPhail, 1982), others have reported a variety of biochemical and functional changes (Sobrian et al., 1989; Woolverton and Johnson, 1992; Spear, 1996; Morrow et al., 2002a) and also, several behavioral alterations in the performance of learning tasks (Smith et al., 1989; Spear et al., 1989; Heyser et al., 1990), in the water maze (Smith et al., 1989), in the forced swim test (Bilitzke and Church, 1992; Molina et al., 1994, 1995; Overstreet et al., 2000), and in displaying neophobic behavior (Johns et al., 1992b). These differences are evident also in locomotor activity (Hutchings et al., 1989; Smith et al., 1989; Church and Overbeck, 1990; Henderson and McMillen, 1990). In the rat, prenatal cocaine exposure was reported to increase activity in the offspring (Henderson and McMillen, 1990), decrease activity (Smith et al., 1989; Church and Overbeck, 1990; Kunko et al., 1993), or not to affect it at all (Foss and Riley, 1991; Riley and Foss, 1991). These seemingly contradictory results may be explained, in part, by methodological differences such as subject age, length of the test session, dose of drug administered (Johns et al., 1992a) and the type of apparatus.

Open-field test is one of the most widely used measures to evaluate changes in locomotor activity, which are positively correlated with emotional reactivity and exploratory behavior (Denenberg, 1969). This test exploits the natural aversion of rodents to a bright and open area (Montgomery, 1955). In this context, a novel situation can produce changes in the emotional state, although repeated experiences may attenuate the emotional response (Kulkarni, 1977). Rats with

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higher emotional state, so called "emotional rats", when exposed to a novel and aversive stimulus display little motor activity and a high defecation rate (Denenberg, 1969; Walsh and Cummins, 1976). The locomotor activity is an indicator of exploratory behavior but it is also a measure for emotional reactivity (Denenberg, 1969). Therefore, high activity on the first day of testing has a positive association with high emotionality, while high activity in subsequent testing days is associated with low emotional reactivity (Denenberg, 1969).

The aim of the present study was to examine the developmental effects of prenatal exposure to cocaine during the first month of life through open-field behavioral testing. With this purpose, the locomotor activity, emotional response and animal habituation to the open-field, were investigated on the end of the second, third and fourth weeks of life, in three consecutive days in each week, covering three key developmental states. These developmental ages correspond to three critical periods of development (Laviola et al., 1992): postnatal day 14 (PND 14) – in the preweaning period, corresponding to the day of eye opening in the strain used (Alder and Zbinden, 1977); PND 21 – the day of weaning; and PND 30 – the end of the critical period for motor development (Walton et al., 1992) and beginning of prepubescent period (Spear, 2000). Both females and males were tested in the open-field, in order to assess any gender differences in the outcomes of prenatal cocaine exposure.

2. Materials and methods

2.1. Subjects and protocol of drug exposure

Rats used in this study were offspring born from Wistar females purchased from the colony of the Gulbenkian Institute of Science, Oeiras, Portugal. They were bred at the Institute of Molecular and Cell Biology, University of Porto, Portugal. Animals were housed in a temperature and humidity controlled colony room maintained on a 12/12 h light/dark cycle, with free access to food and water. At the onset of breeding, adult nulliparous females were mated with one male of the same strain. The morning a copulatory plug or sperm-positive vaginal cytology was observed, was considered as gestational day 1 (GD 1). Pregnant females were weighed, housed individually in standard cages containing wood bedding, and assigned to one of the following prenatal groups: a cocaine-exposed group (CC) and a control group, pair-fed to the CC group (PF). Dams in the CC group received subcutaneous injections (s.c.) of cocaine hydrochloride (Sigma Chemical Co., St. Louis, MO) at 60 mg/kg of body weight/day from GD 8 to 22 and were given ad lib food and water. The period of exposure comprises the major periods of organogenesis and of neurogenesis, migration and gliogenesis, covering also the onset of synaptogenesis (Insel, 1995; Henck, 2002). Each daily dose was divided into two equal parts, administered between 8:30–9:00 a.m. and 5:00–6:00 p.m. Dams in the PF group received daily s.c. injections of vehicle (saline 0.9%), isovolumetric to cocaine and were submitted to food restriction (pair-fed to the cocaine females).

On the day after birth, PND 1, each litter was culled to eight pups, gender balanced, and pups weighed, marked with a felt-tip pen for identification and housed in standard polycarbonate cages, living directly on wooden bedding. Pups were weaned on PND 21. All procedures used were approved by the Portuguese Agency for Animal Welfare (General Board of Veterinary Medicine).

2.2. Behavioral testing: open-field

The open-field consisted of acrylic cubic test arena (0.4 m × 0.4 m × 0.4 m) equipped with two parallel arrays of photocells, one on a lower level with photocells in the *x* and *y* planes and another with photocells only in the *x* plane, and placed at different heights (according to the age of the tested pup), superimposing an invisible grid over the behavioral activity arena (San Diego Instruments, San Diego, CA), which allowed automatical recording of horizontal and vertical activity.

Thirty-two rats (16 from the CC group and 16 from the PF group) from different litters were individually tested in the open-field for three consecutive days, starting on PND 14 (14–16), PND 21 (21–23) and PND 28 (28–30). In each session, the rat was removed from its home cage in the colony room, brought into the adjacent testing room (illuminated with 100 lx and noise attenuated) and placed in the center of the open-field arena. The behavior in the open-field was registered for 15 min. The following behavioral categories were analysed: locomotor activity (i.e. total number of movements); peripheral activity or thigmotatic scanning (i.e. frequency of locomotion along the walls of the open-field); center activity (i.e. frequency of locomotion in the central section of the open-field), and rearing behavior (i.e rat reared on its hindpaws, both on or off the walls). Additionally, the number of faecal boli present in the arena at the end of each session was registered on second (PND 21–23) and third (PND 28–30) set of sessions. The open-field arena was thoroughly cleaned with neutral soap after each test session. The animal habituation to the open-field in each set of three consecutive sessions was analyzed by studying different behaviors between sessions.

2.3. Data analyses

Behavioral data and defecation rate were analyzed by a 3-way analysis of variance (ANOVA) (treatment × gender × session) with repeated measures. Since this ANOVA did not indicate a significant effect of the interaction of gender factor. Data was collapsed across gender and reanalysed by a 2-way ANOVA (treatment × sessions) with repeated measures for each age tested and for each behavior scored in the open-field. This analysis also evaluated the animal pattern of habituation to the open-field. Differences across age throughout development were analyzed by 2-way ANOVA (treatment × age) with repeated measures for each

session. Whenever statistically significant differences were found between treatments or sessions, *t*-test comparisons were used to test the post hoc mean comparisons. Results were analyzed at a significance level of 5% ($p < 0.05$), using the software Statistica version 5.5 (Statsoft Inc., 1999).

3. Results

Prenatal exposure to cocaine significantly altered open-field behavior in developing rat pups offspring. A significant main effect of treatment was observed for total activity on the second (PND 21–23) and on the third (PND 28–30) set of sessions (respectively, [$F(1,30) = 5.98$; $p < 0.05$] and [$F(1,30) = 4.52$; $p < 0.05$]). Within each set sessions, further post hoc analysis of data, revealed that offspring prenatally exposed to cocaine exhibited higher levels of total activity on PND 22 and on PND 29 (respectively, [$t(32) = 11.05$; $p < 0.05$] and [$t(32) = 7.13$; $p < 0.05$]) (Fig. 1A and B). On the first set of evaluations, no significant differences in total activity along the three consecutive sessions (PND 14–16) were found.

For data concerning the first set of three sessions (PND 14–16), ANOVA revealed a significant effect of the different sessions in the rearing behavior [$F(2,60) = 7.03$; $p < 0.05$] and a significant interaction between treatment and session [$F(2,60) = 3.58$; $p < 0.05$]. The analyses of animal habituation to the open-field throughout sessions showed that on

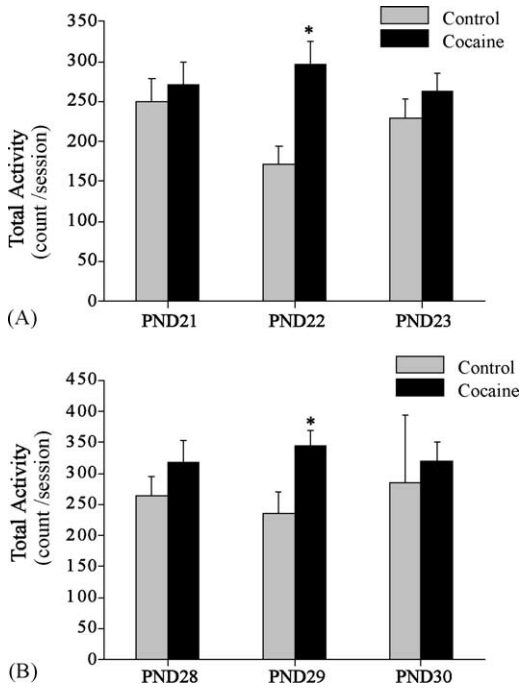

Fig. 1. Total activity in the open-field. (A) Data obtained along the third postnatal week (PND 21–23); (B) data obtained along the fourth postnatal week (PND 28–30). The data represent the mean plus standard error of the mean (S.E.M.) expressed as arbitrary activity counts per session of 15 min. *Significantly different from control ($p < 0.05$).

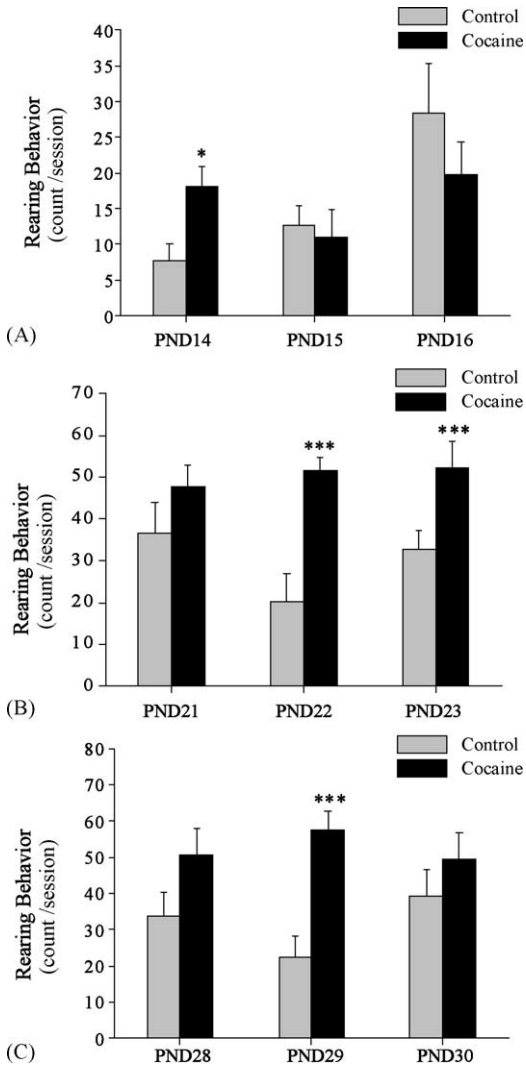

Fig. 2. Rearing behavior in the open-field. (A) Data obtained along the second postnatal week (PND 14–16); (B) data obtained along the third postnatal week (PND 21–23); (C) data obtained along the fourth postnatal week (PND 28–30). The data represent the mean plus S.E.M. expressed as rearing counts per session of 15 min. Labelled columns are significantly different from control *$p < 0.05$ and ***$p < 0.001$.

the second week cocaine-exposed animals had a different rhythm of rearing behavior. Prenatal cocaine-exposed pups reared more than control animals on PND 14 [$t(32) = 8.63$; $p < 0.05$], whereas, on PND 16, they reared apparently less. However, this decrease did not reach significance (Fig. 2A). No other behavior category presented a significant main effect of session.

ANOVA showed also significantly altered rearing behavior in rats prenatally exposed to cocaine on the second (PND 21–23) [$F(1,30) = 16.02$; $p < 0.001$] and on the third (PND 28–30) [$F(1,30) = 8.95$; $p < 0.05$] set of sessions. Further testing has shown that rats prenatally exposed to cocaine reared more than PF control animals on PND 22 [$t(32) = 17.71$; $p < 0.001$], PND 23 [$t(32) = 6.36$; $p < 0.05$]) and PND 29 [$t(32) = 7.83$; $p < 0.001$] (Fig. 2B and C).

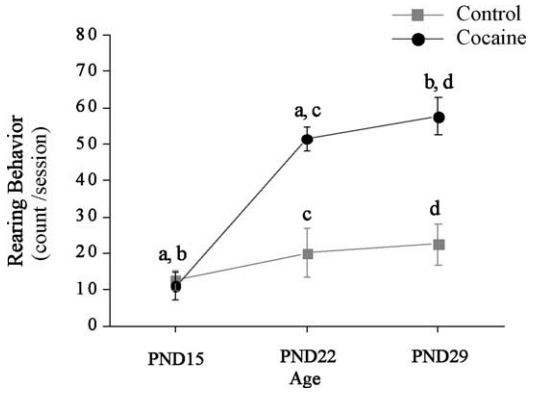

Fig. 3. Rearing behavior in the open-field, data obtained in the second session of each tested week. Values represent the mean plus S.E.M. expressed as rearing counts per session of 15 min; (a) and (b) represent significant differences ($p < 0.001$) between ages within the same group, (c) and (d) represent significant differences ($p < 0.001$) to control values.

Peripheral activity and the number of entries in the center of open-field (central activity) did not differ significantly among groups in the three developmental ages.

For data concerning behavioral differences across sessions throughout development, ANOVA showed a main effect of age in rearing behavior ([$F(2,60) = 18.95$; $p < 0.001$], [$F(2,60) = 30.34$; $p < 0.001$], [$F(2,60) = 7.02$; $p < 0.05$] for the first, second and third session respectively), central activity ([$F(2,60) = 10.36$, $p < 0.001$], [$F(2,60) = 11.49$; $p < 0.001$], [$F(2,60) = 23.77$; $p < 0.001$] for the first, second and third session respectively), peripheral activity ([$F(2,60) = 12.02$; $p < 0.001$], [$F(2,60) = 11.65$; $p < 0.001$], [$F(2,60) = 13.54$; $p < 0.001$] for the first, second and third session, respectively) and total activity ([$F(2,60) = 14.5$; $p < 0.001$], [$F(2,60) = 15.7$; $p < 0.001$], [$F(2,60) = 12.93$ $p < 0.001$] for the first, second and third session respectively). In summary, all recorded behaviors increased its frequency with age.

Rearing behavior was also affected by a significant interaction between treatment and age [$F(2,60) = 13.38$; $p < 0.001$] in the second session of each experimental week. Rats prenatally exposed to cocaine on PND 15 displayed a number of rears similar to control rats, but on PND 22 and 29 these rats showed a much higher level of rearing than the PF group ([$t(32) = 17.71$; $p < 0.001$] and [$t(32) = 2,67$; $p < 0.05$], respectively). Analyses across age within each group showed that rats prenatally exposed to cocaine increased rearing behavior with age (from PND 15 to PND 29 [$t(32) = -7.45$; $p < 0.001$]), whereas in the PF group there was no differences across ages (Fig. 3).

The number of faecal boli was also recorded in the second and third sets of sessions, but differences between groups were not significant.

4. Discussion

In the present study, it was shown that daily cocaine administration of 60 mg/kg body weight from GD 8 to GD 22 produced alterations in the open-field behavior of rats prenatally exposed to this drug. These animals displayed significantly higher levels of total activity at 22 and 29 days of age compared with the pair-fed group. Increased locomotor activity after prenatal cocaine was previously observed after 6 h of testing in the open-field (Henderson and McMillen, 1990). However, in that study, the first 15 min of activity on PND 30 were analyzed separately and showed no significant effect of cocaine exposure. This first period of testing, corresponds, although at a different stage of development, to the first test session of the present experiment, in which the same result was observed. Nevertheless, other authors reported decreased total activity in rats prenatally exposed to cocaine (Smith et al., 1989; Church and Overbeck, 1990; Kunko et al., 1993). Direct comparisons are difficult to establish since those studies employed different routes of administration (intragastric administration, Kunko et al., 1993), a wide range of doses (i.e. 6 mg/kg, Kunko et al., 1993; 40, 60, 80 and 100 mg/kg, Church and Overbeck, 1990; 10 mg/kg, Smith et al., 1989), different ages (animals tested on PND 20, 49, 80–90, Church and Overbeck, 1990; PND 30 and 60, Henderson and McMillen, 1990; PND 25, 30 and 35, Smith et al., 1989), different observation periods (6 h, Henderson and McMillen, 1990; 30 min, Smith et al., 1989), different number of test sessions and different types of open-field apparatus (Automex “S activity meter”, Henderson and McMillen, 1990). Alterations in the global activity are known to reflect changes in the dopaminergic and serotonergic systems, which were described to be triggered by prenatal exposure to cocaine either by altering the levels of dopamine and serotonin in several brain areas (Henderson and McMillen, 1993; Keller et al., 1994; Keller and Snyder-Keller, 2000; Yan, 2002), by interacting with the standard development of the dopamine and serotonin transporters and receptors (Dow-Edwards et al., 1990; Scalzo et al., 1990; Henderson et al., 1991; Leslie et al., 1994; Choi et al., 1998a), or by altering dopaminergic neurons (Minabe et al., 1992; Morrow et al., 2001). Exposure to cocaine following the same protocol used in the present work, was shown to alter the patterns of neuronal migration resulting in abnormal architecture of the hippocampus and cortical sections (Baraban et al., 1999) and to increase the density of neurons on the prefrontal cortex on PND 14 (Tavares and Silva, 1996). The hippocampus and cortical areas are implicated in memory and cognition. Thus, interfering with these structures would be expected to cause behavioral alterations, which would mainly be reflected in the performance of rats in the second and third open-field sessions of each tested age, as these sessions imply a component of learning and habituation. In fact, in the present work, total activity was significantly increased on PND 22 and PND 29.

Cocaine administration to animals and humans may cause fear and panic-like behaviors (Mayes et al., 1998; Blanchard and Blanchard, 1999), and as peripheral activity is considered an index of timidity (Denenberg, 1969), central activity could be a useful indicator of fear reduction and higher exploration. In this sense, it would be expected that rats prenatally exposed

to cocaine would go to the center significantly less than controls and would have higher frequency of peripheral activity. However in this study, no significant differences were found in peripheral and central activity of offspring prenatally exposed to cocaine.

Besides horizontal locomotion, the behavioral response of rats to novelty is also characterized by rearing behavior (vertical activity). The rearing behavior, as a behavioral response to novelty, is considered to reflect not only exploratory activity, but also emotionality (Thiel et al., 1999). On PND 14, this behavior was increased in rats prenatally exposed to cocaine, during the first open-field session; which was the first time that these animals experimented the open-field arena. Therefore, the present data suggest that rats prenatally exposed to cocaine were more emotional when in contact with the open-field for the first time than control animals. High activity on the first performance in the open-field was said to be more related with high emotionality than with low emotionality (Denenberg, 1969). Conversely, the increased rearing behavior displayed on PND 22, 23 and 29 in rats exposed to cocaine during prenatal life, may be related with higher global activity and/or reduction of fear, which can indicate that offspring of cocaine-exposed dams start displaying exploratory behavior only after several exposures to the open-field arena. Fear and anxiety are under control of the limbic system, mainly the amygdala and the nucleus accumbens are limbic structures involved in emotional control (Levant, 1997; Missale et al., 1998). Prenatal exposure to cocaine was shown to decrease the metabolism (Dow-Edwards et al., 1990), and to increase the expression of c-fos in the amygdala (Snyder-Keller and Keller, 2001; Morrow et al., 2002b; Mitchell and Snyder-Keller, 2003), affecting its standard development and possibly inducing deficient function of this area, which may account for fear reduction. Recently, 1-week pups prenatally exposed to cocaine were shown to present reduced serotonergic innervation in the nucleus accumbens and striatum (Yan, 2002), matching the alterations previously described for the dopaminergic system (Scalzo et al., 1990; Collins and Meyer, 1996; Coulter et al., 1996; Giustino et al., 1998; Glatt et al., 2000; Salvatore et al., 2004). These altered patterns of development of the serotonergic and dopaminergic mesolimbic structures are probably related to the altered patterns of activity observed in the present study, since the nucleus accumbens is involved the activation of locomotor activity, while the striatum is implicated in controlling the patterns of motor activity (Voorn et al., 1988; Robbins and Everit, 1992; Calabresi et al., 2000).

On PND 22 and 29, rats prenatally exposed to cocaine showed higher activity levels than controls. In fact, cocaine animals were generally more active during the three set of sessions than controls, however, the significant increased activity observed on the second sessions of both the second and third experimental weeks (PND 22 and 29), may be more related to the decrease of activity (when compared to PND 21 and 28, respectively) observed in rats of the PF control group, and may indicate that rats of PF control group were more rapidly habituated to the open-field.

The defecation rate is related with the emotional reactivity (Denenberg, 1969; Walsh and Cummins, 1976). This parameter was analyzed and results did not show any significant differences on the defecation rate between cocaine and PF groups. In this study, the scores of defecation were only registered on the second (PND 21–23) and third (PND 28–30) set of sessions, since on PND 14 (PND 14–16), when animals contact for the first time the open-field, there is rarely defecation. The lack of differences in this parameter may be associated with the fact that the defecation scores started to be registered when animals were placed in the open-field for the fourth time. The repeated exposure to the open-field increased the animal's familiarity and habituation to this environment and consequently reduced fear (Walsh and Cummins, 1976).

In the present study, prenatal cocaine treatment did not affect behavioral responses to the open-field in a gender-dependent way. However, other studies using similar experimental protocols have found gender differences in locomotor activity (Dow-Edwards, 1989; Brunzell et al., 2002a) as well as in other behavioral patterns (Church and Overbeck, 1990; Choi et al., 1998b; Brunzell et al., 2002b). Also, gender differences in the outcomes of prenatal cocaine exposure are clearly observed in several neurochemical and biochemical parameters, such as brain metabolism (Dow-Edwards et al., 1990, 2001), mesolimbic dopamine function and dopamine turnover (Minabe et al., 1992; Miller et al., 1995; Giustino et al., 1998), or response to a cocaine challenge dose in the adult rat (Miller and Seidler, 1994). The fact that no differences between males and females were observed in the present study does not mean that gender differences would not be evident if these rats were tested in the adulthood, since most studies report behavioral differences only at this stage.

The open-field behavior increased with age in the two groups. This increased activity in young rats can be a consequence of increased familiarity with the environment and/or a manifestation of maturation per se (Bronstein, 1972). Results also showed that rats exposed to cocaine during prenatal life increased rearing behavior throughout development.

In conclusion, the present study provides evidence that prenatal cocaine exposure alters the open-field behavior of rats during the early postnatal life. Rats prenatally exposed to cocaine are more emotional on the first exposure to the open-field and present a delay on the onset of exploratory behavior in the open-field arena, which may indicate that they take longer to become habituated to a novel and open environment. These effects of prenatal cocaine exposure indicate consequences on the way animals explore and gather environmental information, interfering with the standard pattern of cognitive development.

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