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Original article

Effect of neonatal nociceptin or nocistatin imprinting on the brain concentration of biogenic amines and their metabolites

Kornélia Tekes [a], Melinda Gyenge [a], Péter Sótonyi [b], György Csaba [c,*]

[a] Department of Pharmacodynamics, Semmelweis University, P.O. Box 370, H-1445 Budapest, Hungary
[b] Department of Cardiovascular Surgery, Semmelweis University, P.O. Box 370, H-1445 Budapest, Hungary
[c] Department of Genetics, Cell and Immunobiology, Semmelweis University, P.O. Box 370, H-1445 Budapest, Hungary

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Abstract

Noradrenaline (NA), dopamine (DA), homovanillic acid (HA), serotonin (5HT) and 5-hydroxyindole acetic acid (5HIAA) content of five brain regions (hypothalamus, hippocampus, brainstem, striatum and frontal cortex) and the cerebrospinal fluid (CSF) was measured in adult (three months old) male and female rats treated neonatally with a single dose of 10 μg nociceptin (NC) or 10 μg nocistatin (NS) for hormonal imprinting. The biogenic amine and metabolite content of cerebrospinal fluid was also determined. In NC treated animals the serotonergic, dopaminergic as well as noradrenergic systems were influenced by the imprinting. The 5HT level increased in hypothalamus, the 5HIAA tissue levels were found increased in hypothalamus. Hippocampus and striatum and the HVA levels increased highly significantly in brainstem. Dopamine level decreased significantly in striatum, however in frontal cortex both noradrenalin and 5HIAA level decreased. Nevertheless, in NS-treated rats decreased NA tissue levels were found in hypothalamus, brainstem and frontal cortex. Decreased DA levels were found in the hypothalamus, brainstem and striatum. NS imprinting resulted in decreased HVA level, but increased one in the brainstem. The 5HT levels decreased in the hypothalamus, brainstem, striatum and frontal cortex, while 5HIAA content of CSF, and frontal cortex decreased, and that of hypothalamus, hippocampus and striatum increased. There was no significant difference between genders except in the 5HT tissue levels of NC treated rats. Data presented show that neonatal imprinting both by NC and NS have long-lasting and brain area specific effects. In earlier experiments endorphin imprinting also influenced the serotonergic system suggesting that during labour release of pain-related substances may durably affect the serotonergic (dopaminergic, adrenergic) system which can impress the animals' later behavior.

Keywords: Hormonal imprinting; Biogenic amine; Brain; Nociceptin; Nocistatin

1. Introduction

The first encounter between the developing hormone receptor (hormonal imprinting) and the target hormone at neonatal age basically influences the maturation and later binding capacity of receptors [1–4] as well as the hormone production of the targeted cells in the adult animals [5]. However, not only the production of the imprinter hormone is setting, but that of the molecules related chemically or functionally as well as those ones that participated in the execution of the same function [6,7].

In earlier experiments some connections were demonstrated between the endorphin imprinting and adult brain serotonin level as well as plasma or cerebrospinal fluid (CSF) nocistatin levels [7,8]. These results allowed the supposition that different pain-controlled endorphin release during delivery durably influences later pain tolerance and behavior. In the present experiments we wanted to study the effect of neonatal imprinting by the other two pain-regulating endogenous

* Corresponding author. Tel./fax: +36 1 210 2950.
E-mail address: csagyor@dgci.sote.hu (G. Csaba).

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neuropeptides, nociceptin (which is increasing pain) and nocistatin (which reduces pain) on the levels of biogenic amine neurotransmitters and their metabolites in different brain areas and the CSF.

2. Materials and methods

2.1. Animals and treatment

Wistar rats of our (Charles River originated) closed breeding colony were housed at room temperature under normal light cycle. Standard laboratory food and water were available *ad libitum*. Newborn (within 24 h after birth) male and female rats were treated subcutaneously with a single dose of 10 μg nociceptin (Bachem, Bubendorf, Switzerland) or 10 μg nocistatin (Bachem) dissolved in normal saline. Controls got only the vehicle. When the animals were three months old, cerebrospinal fluid was drawn through *foramen occipitale magnum* from animals in ether anesthesia and five regions of the brain (frontal cortex, hypothalamus, hippocampus, striatum and brain stem) were dissected on a 0 °C aluminum surface. The samples were kept frozen at −80 °C. Noradrenaline (NA), dopamine (DA), homovanillic acid (HVA), serotonin (5HT) and 5-hydroxyindole acetic acid (5HIAA) were determined in the specimens by validated HPLC-EC method. The values with the standard deviations (SD) are summarized in the tables and are means of 5–8 animals both in the imprinted and control groups of rats. Values under the limits of quantitation (LOQ) of the method are not shown.

2.2. Determination of the biogenic amines and their metabolites

Chemicals were purchased from commercial sources in the best available quality.

Samples were analyzed by reversed phase high-performance liquid chromatography with electrochemical detection (HPLC-EC) consisting from a Jasco pump (PU1580, Tokyo, Japan) connected to a Decade amperometric/electrochemical detector (Antec, Leyden, Netherlands). Samples were injected directly using a 50 μl loop and separation was carried out at 30 °C, at Eox 0.65 V, with sensitivity of 10 nA on Zorbax RX-18 4.6 × 250 mm (5 μm) analytical column using a Zorbax RX-C18 4.6 × 12.5 mm (particle size 5 μm), Agilent (USA) pre-column with a time filter of 0.1 s. The mobile phase contained 56.2 mmol/L Na_2HPO_4, 47.9 mmol/L citric acid, 0.027 mmol/L Na_2EDTA, 0.925 mmol/L octane sulfonic acid, and 75:950 acetonitrile/phosphate buffer. The flow rate of the mobile phase was 1 mL/min. The pH was adjusted to 3.7 with 85% H_3PO_4. Chromatograms were electronically stored and evaluated using a Borwin 1.21 chromatographic software (JMBS, Le Fontanil, France).

2.3. Sample preparation

From the CSF samples aliquots of 50 μl were treated with 150 μL of 0.8 M perchloric acid (PCA), then centrifuged with 10,000g for 10 min at 4 °C in an Eppendorf centrifuge (A. Hettich, Tuttlingen, Germany). The brain samples were homogenized in four volume of 0.8 M PCA by an Ultra Turrax T25 Janke&Kunkel homogenizer at 20,000 rpm/min for 10 s (IKA Labortechnik, Staufen, Germany) then the homogenates were centrifuged in the Eppendorf centrifuge by 14,000*g* for 10 min at 4 °C (A. Hettich, Tuttlingen, Germany) the supernatants gained were used for HPLC analysis. Samples were kept at −80 °C before their analysis. Data are given in ng/mL ± SD, or ng/mg wet tissue ± SD, as indicated.

3. Results

It was found that in the hypothalamus of both males and females neonatal nociceptin as well as nocistatin imprinting resulted in significant changes particularly in the serotonergic system. Following three months of nociceptin imprinting significantly elevated 5HT and 5HIAA levels were measured in both sexes. However, neonatal nocistatin imprinting (Table 1) resulted in extremely decreased 5HT levels in both sexes, while significantly increased 5HIAA levels were found in the treated animals. Hypothalamic DA levels were found unchanged neither in the male nor in female nociceptin-imprinted rats, however nocistatin treatment caused significant decrease in dopamine levels in both sexes compared to the vehicle-treated controls without influencing HVA levels. When effect of nociceptin or nocistatin imprinting was compared on NA tissue levels it was observed that NC levels were not influenced by neonatal NC imprinting neither in males nor in females, however NS imprinting resulted in highly significant decrease in both sexes (Table 1).

In the brainstem nocistatin imprinting resulted in significant changes in the noradrenalin level and also in the dopaminergic and serotonergic system. Nociceptin treatment resulted in significant increase only in HVA tissue level. However, following NS imprinting noradrenalin, dopamine and serotonin levels decreased significantly, while elevated HVA level were measured and females behaved similarly (Table 2).

In the hippocampus both NC and NS influenced only the serotonergic system in both genders resulting in significant increase in 5HIAA levels following imprinting (Table 3). Noradrenalin and 5HT levels are not given (na) being under the limit of quantitation (LOQ) value, namely lower than 1 and 0.67 ng/mg wet tissue, respectively in both the controls and imprinted rats.

In the striatum only NS imprintings affected significantly dopaminergic as well as serotonergic system. It

Table 1
Biogenic amine and metabolite content of hypothalamus in control and nociceptin (NC) or nocistatin (NS) imprinted adult male and female* rats (ng/mg wet tissue ± SD)

Material	Control	NC	Significance to control (p)	NS	Significance to control (p)
NA	1122 ± 227.4	831.8 ± 520.6	n.s.	67.6 ± 12.2	0.0005
DA	270.9 ± 55.4	251.3 ± 35.4	n.s.	37.4 ± 3.9	0.001
HVA	63.8 ± 14.7	75.8 ± 14.9	n.s.	67.4 ± 6.9	n.s.
5HT	64.1 ± 29.7	182.8 ± 75.7	0.01	<LOQ(0.67)	n.a.
5HIAA	155.7 ± 17.3	801.2 ± 171.6	0.001	693.1 ± 81.6	0.000001
NA*	673.5 ± 101.3	832.9 ± 183.6	n.s.	<LOQ(1.0)	n.a.
DA*	217.7 ± 77.7	225.3 ± 52.7	n.s.	34.3 ± 3.2	0.005
HVA*	63.6 ± 8.5	61.4 ± 7.4	n.s.	65 ± 10.5	n.s.
5HT*	75.9 ± 36.9	141.8 ± 51.7	0.02	<LOQ(0.67)	n.a.
5HIAA*	277.7 ± 106	787.6 ± 126.7	0.00001	616.4 ± 94.1	0.0007

NA, noradrenaline; DA, dopamine; HVA, homovanillic acid; 5HT, serotonin; 5HIAA, 5-hydoxyindoleacetic acid; n.s., not significant; n.a., not applicable; LOQ, limit of quantitation.

Table 2
Biogenic amine and metabolite content of brainstem in control and nociceptin (NC) or nocistatin (NS) imprinted adult male and female* rats (ng/mg wet tissue ± SD)

Material	Control	NC	Significance to control (p)	NS	Significance to control (p)
NA	520.8 ± 113.1	591.8 ± 332.2	n.s.	<LOQ(1.0)	n.a.
DA	138.3 ± 45.8	100.9 ± 20	n.s.	<LOQ(0.8)	n.a.
HVA	50.9 ± 3.2	69.2 ± 11.2	0.01	68.1	0.005
5HT	389.2 ± 71.2	340.2 ± 76.8	n.s.	<LOQ(0.67)	n.a.
5HIAA	1081.6 ± 179.4	1302.1 ± 150.4	n.s.	1040.4 ± 203.7	n.s.
NA*	438.2 ± 64.8	367.3 ± 110.3	n.s.	<LOQ(1.0)	n.a.
DA*	125 ± 40.3	90.2 ± 53.3	n.s.	<LOQ(0.8)	n.a.
HVA*	47.6 ± 1.1	140.3 ± 72.5	0.01	73.6 ± 10.4	0.005
5HT*	239 ± 37.5	258.2 ± 79.5	n.s.	<LOQ(0.67)	n.a.
5HIAA*	1061.6 ± 215.6	1214.3 ± 325.7	n.s.	1099.9 ± 140	n.s.

NA, noradrenaline; DA, dopamine; HVA, homovanillic acid; 5HT, serotonin; 5HIAA, 5-hydoxyindoleacetic acid; n.s., not significant; n.a., not applicable; LOQ, limit of quantitation.

Table 3
Biogenic amine and metabolite content of hippocampus in control and nociceptin (NC) or nocistatin (NS) imprinted adult male and female* rats (ng/mg wet tissue ± SD)

Material	Control	NC	Significance to control (p)	NS	Significance to control (p)
NA	<LOQ(1.0)	<LOQ(1.0)	n.a.	<LOQ(1.0)	n.a.
DA	36.7 ± 8.2	46 ± 19.2	n.s.	<LOQ(0.8)	n.a.
HVA	62.2 ± 17.2	47.1 ± 4.1	n.s.	58.2 ± 20	n.s.
5HT	<LOQ(0.67)	<LOQ(0.67)	n.a.	<LOQ(0.67)	n.a.
5HIAA	87.6 ± 29	307.9 ± 28.7	0.000002	345.5 ± 48.5	0.0000005
NA*	<LOQ(1.0)	<LOQ(1.0)	n.a.	<LOQ(1.0)	n.a.
DA*	52 ± 14.2	45.3 ± 13.5	n.s.	<LOQ(0.8)	n.a.
HVA*	43.1 ± 9	45.9 ± 2	n.s.	58.2 ± 20	n.s.
5HT*	<LOQ(0.67)	<LOQ(0.67)	n.a.	<LOQ(0.67)	n.a.
5HIAA*	110.6 ± 22.5	338.2 ± 47	0.0000005	345.5 ± 48.5	0.0006

NA, noradrenaline; DA, dopamine; HVA, homovanillic acid; 5HT, serotonin; 5HIAA, 5-hydoxyindoleacetic acid; n.s., not significant; n.a., not applicable; LOQ, limit of quantitation.

is worthy to note that in both genders only in females and in NS treated rats decreased DA levels, but increased 5HIAA were measured. Decrease in 5HT tissue concentration reached significant level only in NS imprinted animals (Table 4).

In the frontal cortex significant decrease in 5HIAA and NA levels were measured after both treatments. It is noteworthy that in NS imprinted animals (both males and females) the control 5HT tissue levels decreased under the LOQ (0.67 ng/mg wet tissue), however, NC

Table 4
Biogenic amine and metabolite content of striatum in control and nociceptin (NC) or nocistatin (NS) imprinted adult male and female* rats (ng/mg wet tissue ± SD)

Material	Control	NC	Significance to control (p)	NS	Significance to control (p)
NA	<LOQ(1.0)	<LOQ(1.0)	n.a.	<LOQ(1.0)	n.a.
DA	5068.9 ± 1181	5540.1 ± 680.9	n.s.	235.3 ± 127.7	0.0007
HVA	1133.7 ± 135.9	1059.3 ± 122.7	n.s.	1175.8 ± 163.9	n.s.
5HT	182.7 ± 53.4	191.7 ± 47.8	n.s.	<LOQ(0.67)	n.a.
5HIAA	192 ± 69	430 ± 66.7	0.0005	351.8 ± 87.3	0.005
NA*	<LOQ(1.0)	<LOQ(1.0)	n.a.	<LOQ(1.0)	n.a.
DA*	5344 ± 1151	4992.7 ± 1231.9	n.s.	315.6 ± 179.8	0.0005
HVA*	1110.4 ± 112.7	1089.2 ± 118.1	n.s.	1353 ± 128.7	0.01
5HT*	202.1 ± 47.2	169.9 ± 27.7	n.s.	<LOQ(0.67)	n.a.
5HIAA*	187.9 ± 72,2	469.5 ± 83.7	0.00009	307.4 ± 36	0.01

NA, noradrenaline; DA, dopamine; HVA, homovanillic acid; 5HT, serotonin; 5HIAA, 5-hydoxyindoleacetic acid; n.s., not significant; n.a., not applicable; LOQ, limit of quantitation.

imprinting resulted in significant decrease only in males. (Table 5).

When CSF biogenic amine levels were measured only NS imprinting and only in males' HVA and 5HIAA decrease reached significant levels (Table 6).

4. Discussion

Nociceptin, a heptadecapeptide (orphaninFQ) is the endogenous agonist for the OP4/NOP receptor and originates from a large peptide preproOFQ/N both in the central nervous system and the periphery. Regional distribution studies on preproOFQ/N, OP4/NOP receptor and OFQ/N mRNA revealed that they are highly expressed in discrete neuronal sites with a pattern distinct from those of classical opioid peptides. It plays a major role in increasing pain, anxiety, aggressivity, etc. [9,10] by central mechanisms. The other peptide with established biological activity used for imprinting, nocistatin, is also proteolytically liberated from the same large peptide, however it does not bind to the OP4/NOP receptor. Nocistatin was shown to functionally antagonizing the effects of nociceptin [11,12]. Reports provide support for the modulatory role of nociceptinergic system on a wide variety of (neuro) endocrine functions as well as on biogenic amine neurotransmission[13]. During delivery the pain is characteristic (however different, depending on the length and intensity of birth, the size of the baby, etc.) In earlier experiments neonatal treatment by an other pain-regulating molecule, endorphin caused life-long differences in brain biogenic amine (serotonin) levels [8,13]. In the present experiment the effect of nociceptin and nocistatin imprinting were studied, in a broader palette of biogenic amines and their metabolites.

The influence of the treatments was extremely strong. Although the neonatal imprinting in case of both NC and NS was done with a single small dose (10 μg) and the measurements were carried on three months later, many highly significant differences compared to vehicle treated controls could be observed both in CSF and the five regions of the brain studied. The NC imprinting resulted in brain area specific long-term effects on all the three biogenic amine systems. In the hypothalamus sero-

Table 5
Biogenic amine and metabolite content of frontal cortex in control and nociceptin (NC) or nocistatin (NS) imprinted adult male and female* rats (ng/mg wet tissue ± SD)

Material	Control	NC	Significance to control (p)	NS	Significance to control (p)
NA	434.5 ± 37.2	163. ± 20.7	0.0004	98.3 ± 13	0.00001
DA	40.3 ± 6.6	54.2 ± 38.4	n.s.	24.5	n.s.
HVA	56.8 ± 16.1	103.3 ± 54.6	n.s.	58.1 ± 18.4	n.s.
5HT	126.5 ± 43.8	70.4 ± 16	0.05	<LOQ(0.67)	n.a.
5HIAA	457.3 ± 46.1	312.5 ± 50	0.001	330.2 ± 40.2	0.001
NA*	381.4 ± 50.47	173.8 ± 12.8	0.0005	121.7 ± 10	0.0002
DA*	31.2 ± 7.2	30.5 ± 6.9	n.s.	<LOQ(0.8)	n.a.
HVA*	53.1 ± 17.5	45.5 ± 4.3	n.s.	56.7 ± 23.9	n.s.
5HT*	124.1 ± 25.6	92.8 ± 38.5	n.s.	<LOQ(0.67)	n.a.
5HIAA*	509.7 ± 58.3	346.6 ± 53.	0.0009	328.7 ± 64.6	0.001

NA, noradrenaline; DA, dopamine; HVA, homovanillic acid; 5HT, serotonin; 5HIAA, 5-hydoxyindoleacetic acid; n.s., not significant; n.a., not applicable; LOQ, limit of quantitation.

Table 6
Biogenic amine and metabolite content of cerebrospinal fluid in control and nociceptin (NC) or nocistatin (NS) imprinted adult male and female* rats (ng/mg wet tissue ± SD)

Material	Control	NC	Significance to control (p)	NS	Significance to control (p)
NA	13.6 ± 5.5	<LOQ(1.0)	n.a.	<LOQ(1.0)	n.a.
DA	5.3 ± 1.9	<LOQ(0.8)	n.a.	<LOQ(0.8)	n.a.
HVA	26.7 ± 3.5	24 ± 3.7	n.s.	18.3 ± 0.4	0.005
5HT	17 ± 9.2	22.8 ± 11.4	n.s.	9 ± 2.1	n.s.
5HIAA	164 ± 36.4	159 ± 32.7	n.s.	98.9 ± 18.2	0.01
NA*	13.5 ± 5.8	<LOQ(1.0)	n.a.	<LOQ(1.0)	n.a.
DA*	<LOQ(0.8)	<LOQ(0.8)	n.a.	<LOQ(0.8)	n.a.
HVA*	29.9 ± 13	23 ± 5.5	n.s.	19.1 ± 1.9	n.s.
5HT*	16.8 ± 9.5	28.5 ± 15.8	n.s.	23.3 ± 14.5	n.s.
5HIAA*	106.3 ± 51	115.8 ± 40.9	n.s.	99.8 ± 10.4	n.s.

NA, noradrenaline; DA, dopamine; HVA, homovanillic acid; 5HT, serotonin; 5HIAA, 5-hydoxyindoleacetic acid; n.s., not significant; n.a., not applicable; LOQ, limit of quantitation.

tonin content increased, and the metabolite level, the 5HIAA concentration, was also increased. In the hippocampus and striatum 5HIAA levels were also increased. However, in the frontal cortex of male's NC imprinting resulted in decreased 5HT level only in male rats and decreased 5HIAA levels in both sexes. If 5HIAA/5HT ratio, as a measure of the serotonin turnover is calculated (data not shown) it can be summed up that neonatal NC imprinting has long-term effect on serotonergic function.

NC imprinting was also acting on dopaminergic function in both sexes in the brainstem and in the striatum by decreasing striatal dopamine level without effect on its metabolite (HVA) tissue concentration and increasing HVA level in brainstem without effect on dopamine level. Calculating the HVA/DA ratio (turnover) one can suppose, that in the aforementioned two brain areas dopaminergic system is also significantly influenced by neonatal NC imprinting and direction of change is similar in both brain areas, assuming that stimulating one.

The NS imprinting on serotonergic function was extremely strong in both sexes by influencing all the five brain areas studied as well as the 5HIAA and HVA levels in the CSF. It is noteworthy that 5HT tissue levels were decreased in hypothalamus, brainstem, striatum and frontal cortex, while in the hippocampus and the CSF the decrease did not reach the significant level. The serotonin level decrease in the hypothalamus, brainstem and the striatum was accompanied by increased 5HIAA levels suggesting a stimulated serotonergic activity. In the brainstem 5HIAA level did not change significantly, however increased 5HIAA/5HT ratio may indicate serotonergic dysfunction in that brain area as well. In the frontal cortex both 5HT and 5HIAA tissue levels were decreased, so decreased serotonergic activity of the frontal cortex may be assumed. In the CSF decreased 5HIAA levels were observed without significant change in 5HT levels, that may also suggest decreased serotonergic activity in such brain areas that were not studied. 5HIAA is the metabolite of 5HT and HVA is metabolite of DA. It can be expected that in case of a decrease of 5HT level, 5HIAA tissue concentration is increasing. Data presented serve further evidence that the different regions of the brain selectively react to the effect of imprinting. It seems to be very difficult to compare the effect of false imprinting to the results of reports on direct effect of nociceptin or nocistatin treatment. However, it seems likely that our data are in line with the results of direct nociceptin treatments, where increase in the inhibitory serotonergic functions were found [14,15].

In case of dopamine the decrease was characteristic both after NC or NS imprinting. In the striatum only DA level was found decreased following NC treatment, while NS imprinting resulted in decreased DA levels in the hypothalamus and the brainstem as well (Table 4). It is in line with the results of direct experiments as nociceptin inhibits dopamine transport [16] and modulate dopamine release [17–21].

Where noradrenaline concentration moved at all, its direction was always a decrease (Tables 1 and 5). The most expressed decrease was in the hypothalamus, where 20 fold amount was present in the controls related to the nocistatin imprinted animals (Table 1). In direct experiments nociceptin inhibits noradrenaline release [22].

There were no important gender-dependent differences as male and female animals reacted in a similar manner except 5HT levels after NC imprinting, where in the frontal cortex only males showed significantly decreased 5HT level. These data suggest that the imprinting effects are not profoundly influenced by later sex-hormonal differences.

Concerning the cerebrospinal fluid only in NS imprinted rats and only in 5HIAA content was found significant decrease (Table 6). This also support the importance of serotonergic system from the point of view of imprinting.

In earlier experiments imprinting by endorphin (an other member of the pain regulating system) influenced brain serotonin level and consequently aggressivity of

rats were reported [8]. In the present experiments nociceptin and nocistatin imprinting durably and profoundly influenced the brain levels of biogenic amine neurotransmitters and their metabolites in a brain-area specific manner. It would be very difficult to compare the direct effects to the influence of imprinting with the same materials, as the direct data are incomplete and sometimes contradictory. However, it seems well established that the effect of neonatal imprinting has long-term consequences. Based on these data we hypothesize that during labour, its length and intensity as well as the sensitivity of the mother could influence the production (level) of the members of the pain-system [23–26]. It can be supposed that these compounds – by lifelong imprinting – affect the adrenergic, dopaminergic and first of all serotonergic systems of the brain. Although there are data on the relationship between the serotoninerg, dopaminerg, adrenerg systems and the pain system (nociceptin, nocistatin), as e.g. antidepressants have also analgesic effects [27], serotonin have basic role in migraine [28] and visceral pains [29], nociceptin inhibits biogenic amine release [17], the exact mechanism is far from being known. So, the pain modulating consequences of the perinatal imprinting by pain substances can not be forecasted.

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