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## Effect of serotonergic nerves lesion in dorsal and median raphe nuclei on the development of tolerance to morphine analgesia in male rat

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**OBJECTIVES:** The aim of this study was to evaluate the role of central serotonergic system on the development of tolerance to morphine antinociception. **METHODS:** Experiments were performed on adult male wistar rats weighing between 200 and 250 g. The control rats (n=8) had daily i.p. injection of morphine (5mg/kg) and the Hot-Plate test for 30 and 60 min subsequently and record in time (latency time). In the sham and test rats following induction anaesthesia, rats were secured in a stereotaxic frame with ear and incisor bars. Then a guide cannula was implanted into the DRN or MRN separately in rats (n=8). Coordinates for the DRN and MRN were taken according to Paxinos and Watson rat brain atlas. In the sham groups, 30 minutes after i.p. injection desipramine (10mg/kg), 1µl/2min of 5, 7- dihydroxytryptamine vehicle (saline + ascorbic acid 10%) was injected into the nuclei. In test groups after the injection of desipramine, 4µg/1µl/2min of 5, 7-DHT was injected into the nuclei. Daily injection of morphine and Hot-Plate test was performed 5 days after the recovery of the rats. At the end of the experiments in the all rats methylen blue (1%) was injected into the nucleuses, the brains were removed and were fixed in the formalin solution (5%). Thereafter the injection sites were studied histologically. **RESULTS:** The results of this study showed that the tolerance to analgesic effect of morphine in the intact and control groups began almost 10 days after the daily injection of morphine but in DRN and MRN-lesioned rats it occurred at 19<sup>th</sup> and 21<sup>st</sup> days respectively. Data was analyzed and statistically significant differences were found between the test and control ( $P < 0.001$ ) or the sham groups ( $P < 0.05$ ). But there were no significant differences between the intact and the control groups. **CONCLUSION:** In conclusion these findings show that the serotonergic nerves lesion delay development of tolerance to morphine analgesia and decline the need for increasing analgesic dose of morphine to obtain the early effects of morphine.

**Key words:** Serotonergic system, Raphe nucleus, Morphine, Tolerance.

sham	( mg/kg)	(n= ) ( )	(Latency Time)			
/ µl/min	5, 7-DHT	4µg/1µl	(5, 7-DHT)	-	1µl	(10mg/kg)
	MRN	DRN	5,7-DHT			
	(p<0.001)					(p<0.05) sham

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DRN

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( ) c

( )

(.)

( )

5-HT<sub>1A</sub>

(.)

( )

( )



( )

(.)

( ± °C)

CNS

( )

(.)

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(Sigma, St.Louis, MO)

(Sigma, St.Louis, MO) (5, 7-DHT)

(Disinhibition)

(TEMAD CO.,Tehran, Iran)

(.)

(Kela n.v., Hoogstraten, Belgium)

μ

(% / )

( / mg/ml)

(.)

5, 7-DHT

DRN

mean L.T. ± S.E.M.

$$\text{MPE\%} = \frac{(\text{TL} - \text{BL})}{(50 - \text{BL})} \times 100$$

MPE= Maximum Possible Effect

TL= Test Latency time

BL= Base Latency time

TL BL

DRN

V: -7.4mm L: ± 4.0mm AP: - 7.64mm

MRN

V: -9.0mm L: ± 4.0mm AP: - 7.64mm

AP)

L

V

%

%

MRN

mm

DRN

mm

( )

MPE% Mean L.T. ± S.E.M.

5, 7-DHT

One way ANOVA

mg/kg

p < 0.05

Tukey

μl

) 5, 7-DHT

μg/ μl

(sham

/ l/min

(

### Latency Time

(intact)

### Hot-Plate

mg/kg

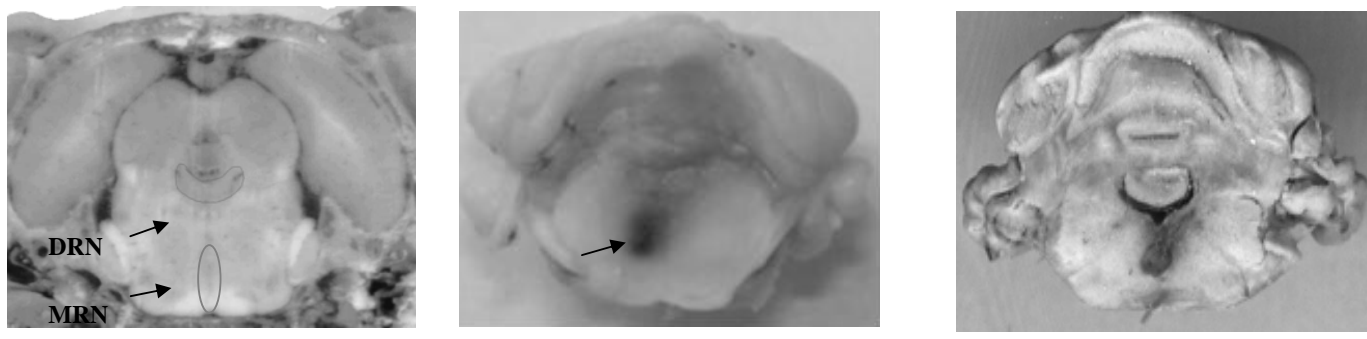
(Latency Time=L.T.)

L.T.

(cut-off time)

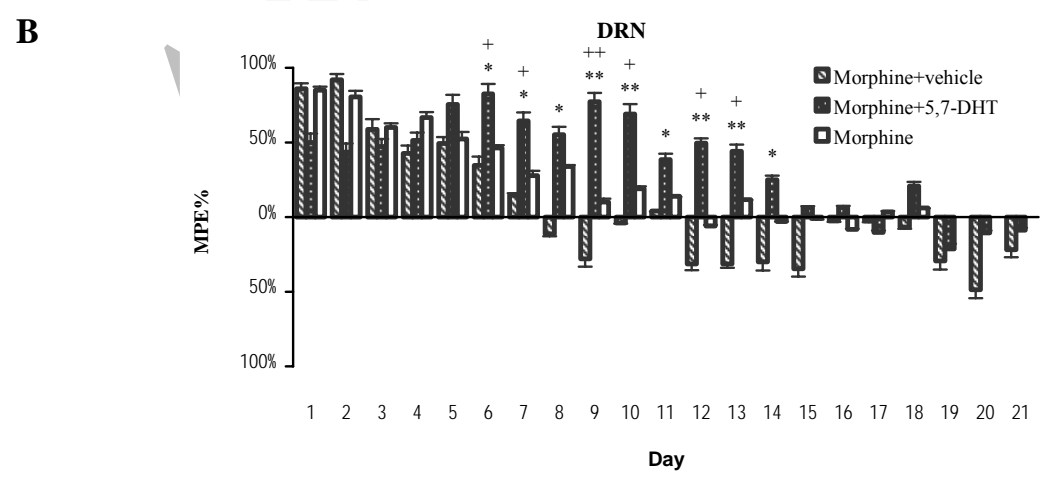
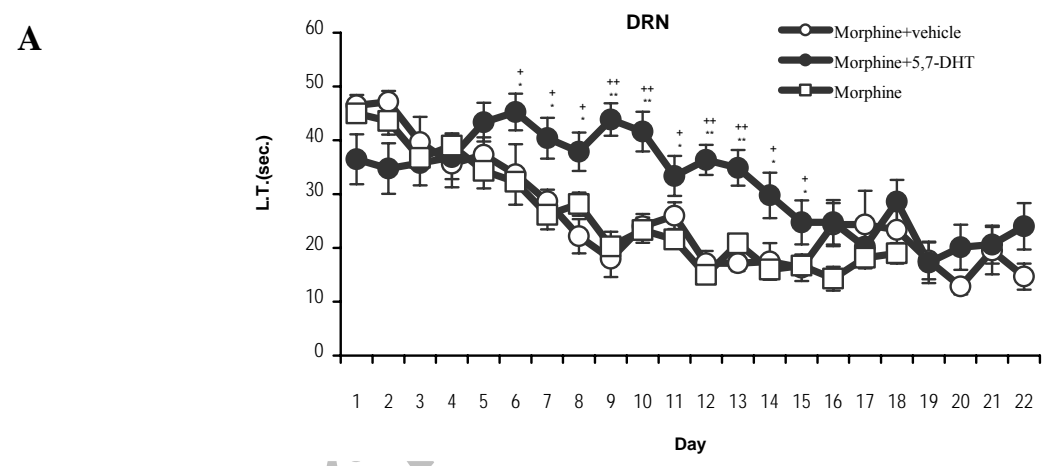
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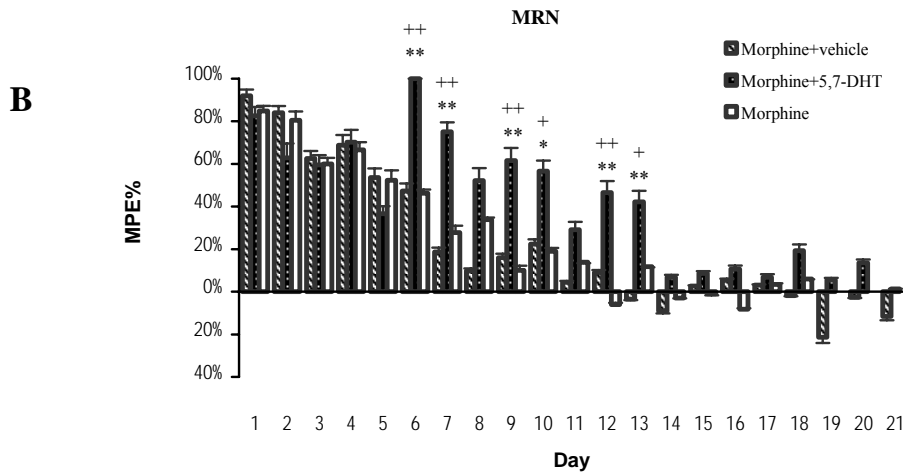
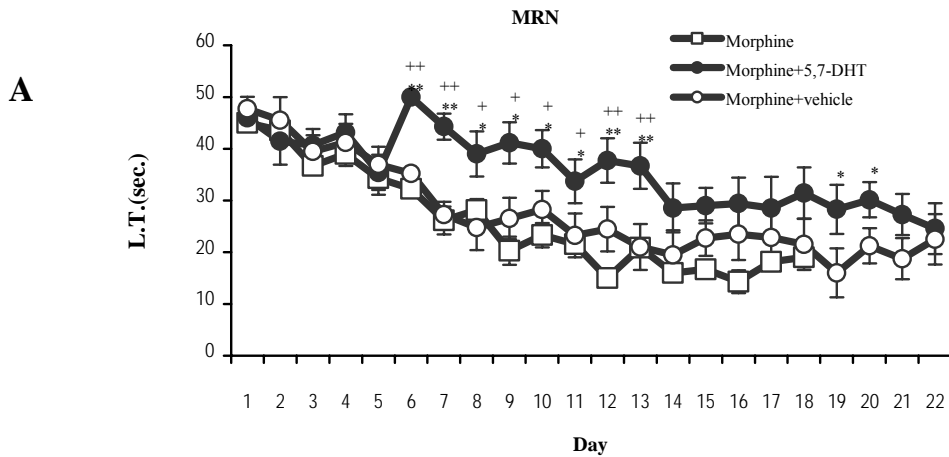


**A** : MRN **B** : DRN **C** : A -

/ ± /	/ ± /	/ ± /	± /	/ ±	±	/ ± /	/ ±	/ ±	/ ± /	Means±S.E.M.
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(A) L.T. (sec.) (B) MPE% (A) (mg/kg, i.p.) (morphine+5,7-DHT) (morphine) DRN (morphine+vehicle) sham \*\* P < 0.001 \* P < 0.05 .



( mg/kg, i.p.) (morphine+5, 7-DHT) (morphine) (MRN) (B) MPE% (A) L.T. (morphine+vehicle) sham

\*\* P < 0.001 \* P < 0.05 †† P < 0.001 † P < 0.05

**MRN** : **DRN** :

MRN 5, 7-DHT 5, 7-DHT DRN 5,7-DHT DRN 5, 7-DHT

( ) ( ) ( ) ( ) ( ) ( ) ( ) ( )

MRN (MRN) (P < 0.001) (P < 0.05) (MRN) ( ) ( ) ( ) ( )

DRN (P < 0.05) DRN (P < 0.001) ( ) ( ) ( ) ( )

( )<sup>1</sup>SSRIs (5, 7-DHT)  
 (MRN DRN) CNS

( ) ( )  
 ( )

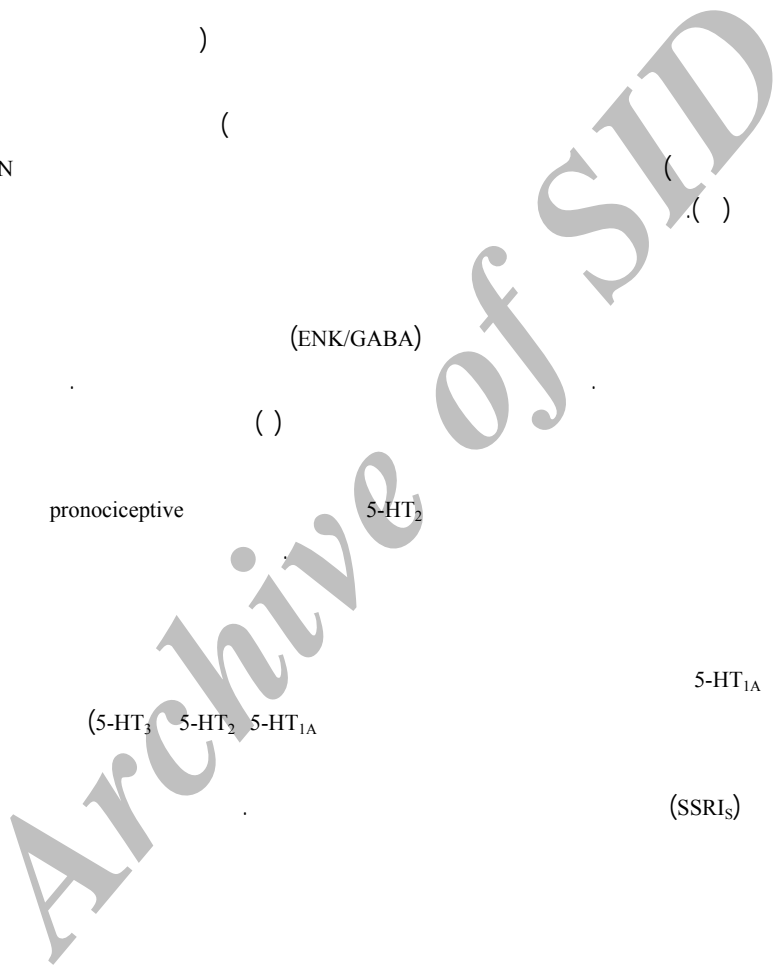
( ) ( )  
 MRN DRN ( )

/ (ENK/GABA)

( )  
 pronociceptive 5-HT<sub>2</sub> 5-HT<sub>2</sub> 5-HT<sub>3</sub>

) ( )  
 (5-HT<sub>3</sub> 5-HT<sub>2</sub> 5-HT<sub>1A</sub>) 5-HT<sub>1A</sub>

(SSRIs)



<sup>1</sup> SSRIs = Serotonin Specific Reuptake Inhibitors

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