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Influence of Demoxytocin on the Behavioural Actions of Melatonin

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Abstract

Oxytocin is stored and released by the posterior pituitary gland. In this study, the influence of oxytocin agonist, demoxytocin pretreatment on the behavioural actions of melatonin was ascertained. Swiss albino mice (n=6) were used for this study as control and test groups. Demoxytocin was injected in a concentration of (20 I.U/kg, i.p) and melatonin was injected (200µg/kg, i.p) 30 minutes before experimentation. The effect of pretreatment with demoxytocin was evaluated after melatonin injection on motor-coordination and locomotor activity. The results of our study suggest that demoxytocin was not able to affect significantly the actions on motor co-ordination but attenuated the locomotor activity after melatonin treatment.

Introduction

Oxytocin has been shown to have a role in social separation and related stress. Oxytocin serves important roles in behaviour regulation and plays important role in emotional and social bonding (Landgraf, 1995). Oxytocin receptor is expressed in the central nervous system and is a G protein coupled receptor. Demoxytocin also known as deamino-oxytocin is an agonist of oxytocin with almost similar profile but some difference in pharmacokinetics and affinity for the oxytocin receptor. The effects of demoxytocin on behavioural aspects have not been studied well and there are few documented reports. On the other hand, melatonin is a ubiquitous natural neurotransmitter like compound and released by the pineal gland. Melatonin has been shown to modify the stress response and aging process and regulates a variety of physiological and neuroendocrine functions through activation of G protein coupled receptors in target tissues (Dubocovich, 1995). Melatonin is expressed in the brain (Cardinali, 1981) and has multifaceted roles in physiology of circadian rhythm (Al-Ghoul, 1998). In this study, we have evaluated the influence of oxytocin agonist, demoxytocin on the motor coordination and open field locomotor activity in mice after treatment with melatonin.

Materials and Methods

Experiments were performed on Swiss albino mice weighing 25-35g and belonging to either sex. They were obtained from Institutional Animal Centre of Christian Medical College, Vellore, India. Animals were divided into groups of 6-8 and kept in separate polypropylene plastic cages under hygienic conditions, lined with paddy-husk bedding. These animals were housed in a colony room under controlled temperature (25±1°C), relative humidity of (60±2%) and were exposed to a 12-h dark cycle, with food and water available *ad libitum*. All experiments were conducted during the light phase between 9.00 a.m. and 4.00 p.m. The experimental protocol

was approved by the Institutional Review Board (IRB) and care of animals was taken as per guidelines of CPCSEA, Department of Animal Welfare, Government of India.

Drugs and Chemicals

Melatonin tablets were obtained from Aristo Pharmaceuticals Pvt. Ltd., Nani Daman, Daman (U.T) and demoxytocin tablets (Sandoz Pharma., Switzerland) were obtained from a local pharmacy store. 0.9 % Saline was obtained from CMCH pharmacy, Vellore.

Methods

A) Rota-rod Test (Motor Co-ordination in mice): Rota-rod test is often used with the apparent assumption by the experimenters that it is a straightforward and simple assay of motor coordination. A Rota-rod tread mill device (Inco, India) was used for the evaluation of the effect of drugs on the motor coordination at speed of 20 rotations per minute. Twenty minutes after administration of demoxytocin (20 IU/kg) i.p and later 30 minutes after melatonin (200µg/kg) i.p was injected. Each mouse was placed on the rotating rod for 5 min (300 secs). The endurance time for each mouse i.e the time mice fell off from the rota rod was noted.

B) Loco-motor Activity Test: The loco-motor activity of albino mice weighing between 25- 35 g were evaluated in an open field loco-motor box made of wood with dimensions (24×24×5) inch and comprising of 16 squares. Loco-motor activity was estimated visually counting the no. of squares the animals crossed in 6 mins. Mice were injected with one of the test drugs or its vehicle and were placed in holding cage for 20 minutes for demoxytocin and 30 minutes for melatonin before testing. Each animal was tested once for the loco-motor activity (Tyagi and Jose, 1999).

C) Statistical Analysis: For statistical evaluation of results and significance testing of group differences, the nonparametric Mann-Whitney U-test and Wilcoxon W test was performed. Results were considered to be of statistical significance at $P \leq 0.05$ (95% confidence interval). Data are presented as Means \pm S.E.M.

Results

Table 1: Effect of demoxytocin and melatonin on the locomotor activity in mice. * denotes the significant values ($P < 0.05$).

Pretreatment	Treatment	Locomotor Activity	% Change
Saline	Saline	99.2 \pm 4.9	
Saline	Demoxytocin	76.6 \pm 3.7	22.78*
Saline	Melatonin	89.8 \pm 7.3	9.47
Demoxytocin	Melatonin	70.5 \pm 5.6	28.93*

Table 2: Effect of demoxytocin and melatonin on the motor co-ordination in mice.

Pretreatment	Treatment	Fall of time (Secs)	% Change
Saline	Saline	95.8 \pm 3.7	
Saline	Demoxytocin	84.2 \pm 5.8	12.10
Saline	Melatonin	86.1 \pm 6.3	10.12
Demoxytocin	Melatonin	83.7 \pm 7.1	12.63

Discussion

Demoxytocin is a synthetic analogue of oxytocin used orally for induction of labour. It has a difference in its biological potency although many of its biological effects are similar to oxytocin (Gazis et al, 1980). We treated the animals with demoxytocin injections and also in combination with melatonin. The results of our study are depicted in Table 1 & 2. As it is clear from Table 2, demoxytocin did not appreciably affect the motor coordination although it did affect locomotor activity suggesting some central role in the oxytocinergic neurons/receptors in the brain (Urry, 1987). On the other hand, melatonin, the main hormone secreted by the pineal gland, mediates a variety of cellular, neuroendocrine and physiological processes; besides, melatonin displays through different mechanisms a protective role against damage caused by free radicals (Shaji & Kulkarni, 1998; Reiter, 1995). After systemic administration, melatonin crosses rapidly the blood-brain barrier and is distributed to the cerebrospinal fluid and throughout the different regions of the brain (Vitte *et al.*, 1988). Melatonin was able to affect the locomotor activity and motor co-ordination more potently, based on our results and this can be attributed to the inhibitory effects in the hippocampus and synaptic potentiation in dorsal horn of spinal cord (Ruben Soto Moyano *et al* 2006). A role for GABAergic mechanism has been speculated for these effects (McNamara, 1996). Demoxytocin does not affect the motor coordination and was ineffective in modulating the actions of melatonin thus suggesting a lesser affinity for oxytocin receptors than its parent compound i.e oxytocin.

Thus this study implicates that the ability of melatonin to modulate neuronal activity may account for many of its physiological actions of melatonin on the central nervous system, it is also conceivable that magnification of these effects when higher, pharmacological doses of the hormone

The results of our study are depicted in Table 1 and Table 2. As depicted in the Table 1, pretreatment with demoxytocin (20 IU/kg i.p) caused a substantial decrease in locomotor activity following treatment with melatonin (28.93 %) and this was found to be statistically significant. On the other hand pretreatment with demoxytocin did not significantly affect motor co-ordination following melatonin treatment as depicted in Table 2.

are administered, could result in altered function of some central neurons such as those involved in long-term synaptic potentiation but it can be safely co-administered with oxytocin analogues in a possible clinical scenario.

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