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Tramadol Potentiates Vasopressin Induced Analgesia in Albino Mice

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Abstract

The effect of centrally acting opioid analgesic Tramadol on vasopressin induced analgesia was evaluated in Swiss albino mice. Analgesia was evaluated in the mice using tail clip and writhing test techniques. Animals were divided into control and test groups (n=6). Arginine vasopressin (12 µg/kg i.p) and its synthetic analogue, Terlipressin (300 µg /kg i.v) injected in the mice produced analgesia by increasing the latency period by 131.6% and 53.5% respectively and reduced the acetic acid writhing by 45.85 % and 13.51 % respectively. Pretreatment with Tramadol (10 mg/kg i.p) potentiated the analgesic action of vasopressin and terlipressin and increased the latency period and reduced the acetic acid induced writhings respectively. This study suggests that Tramadol can be combined with vasopressin for enhanced analgesic effect.

Key Words: Arginine vasopressin, Terlipressin, Analgesia, Writhing, Mice

Introduction

Analgesics are agents that relieve pain by elevating the pain threshold with out affecting conciousness (or) alter other sensory modalities. There are several methods adapted to study pain mechanisms. Some simple techniques include the tail clip, tail flick and writhing technique. Pain stimulation enhances paraventricular nucleus (PVN) mediated synthesis and secretion of arginine vasopressin (AVP). Yang *et al* [1] showed that PVN and peri-aqueductal gray matter (PAG) play a significant role in pain modulation.

On the other hand, pituitary peptide hormone vasopressin has been implicated in the analgesic mechanisms and mediates analgesic effect in the mouse [2,3]. Vasopressin is released in circulation during stress [4]. It has been suggested that endogenous opioids may modulate the vasopressin release in man [5] and rodents [6]. Tramadol, a synthetic analogue of codeine is a centrally acting analgesic with additional non-opioidergic mechanisms.

This study was conducted to ascertain the effect of Tramadol pretreatment on the analgesic activity of vasopressin and its synthetic analogue Terlipressin in Swiss albino mice.

Materials and Methods

Animal maintenance: Swiss albino mice weighing between 25-30 g were used for this study. Animals were housed in groups of 6-8 animals in propylene plastic cages under hygienic conditions, lined with paddy-husk bedding. All experiments were conducted during light phase between 8.00 and 13.00 hrs. All procedures were conducted according to the guidelines of the International association for the study of pain [7].

Drugs and chemicals: Tramadol HCl (Sarabhai Chemicals, Baroda, India), Arginine vasopressin (Samarth Pharmaceuticals Co., Ltd, India), Normal Saline (E.Merck Ltd, India), Terlipressin (Ferring, Denmark), Acetic acid (Qualigens, India).

Determination of Analgesic activity

Haffner's Tail Clip Method: This technique first described by Haffner in 1954 [8] is a simple technique. Here a steel tail clip is applied to the root of the tail of mice to induce pain. Mice that responded to the noxious stimuli by turning or biting the clip with in 15 seconds are used for the test.

Writhing Test: The writhing (Abdominal constrictions) test is used to measure the changes in pain threshold to a chemical stimulus e.g the injection of acetic acid (0.6%; 0.25ml i.p). Analgesia is assessed in mice by noting the abdominal constrictions and a decrease in these constrictions is indicative of analgesic action.

Statistical analysis: The results are expressed as mean ± SE from n=6 observations. The statistical significance ($P<0.05$) was ascertained by ANOVA and Mann-Whitney U Test.

Results

The results of our study are shown in Table 1. AVP and Tramadol showed significant analgesic activity i.e 131.6 % and 73.4 % change in latency period 45.85 % and 65.93% reduction in writhings as per our observations on tail clip and abdominal writhing. However, Terlipressin showed less analgesic activity comparatively 53.5 % and 13.51% respectively. Tramadol pretreatment potentiated the analgesic effect of AVP and Terlipressin as per our observations of the tail clip and writhing tests.

Table 1: Effect of treatment with AVP (12µg/kg i.p) and Terlipressin (300µg/kg i.v) alone and in combination with Tramadol (10 mg/kg i.p) on the analgesic activity in mice. Numbers given in the parentheses below the percentage values describe comparisons of groups for statistical significance

No. (n=6)	Pre-treatment	Treat-ment	Tail clip test (secs)	% change	'P'value	Writhing Test (counts)	% change	'P'Value
1	Saline	Saline	10.5 ± 9.85	-	-	33.67± 3.09	-	
2	Saline	AVP	24.3± 1.9	131.6	<0.01 (1:2)	18.23± 2.45	45.85 (1:2)	<0.05
3	Saline	Terli-pressin	16.11 ± 1.1	53.5	<0.05 (1:3)	29.12 ± 3.41	13.51 (1:3)	>0.05
4	Saline	Tramadol	18.2 ± 1.53	73.4	<0.05 (1:4)	11.47± 2.91	65.93 (1:4)	<0.01
5	Tramadol	AVP	25.56± 1.61	143.5	>0.05 (2:5)	11.08 ± 1.71	67.09 (2:5)	<0.05
6	Tramadol	Terli-pressin	20.59± 1.23	96.15	<0.05 (3:6)	21.34 ± 3.79	36.62 (3:6)	<0.05

Discussion

The results of our study clearly show that the analgesic action of vasopressin analogues in the mice as determined by tail clip and writhing method. The results of our study suggest that AVP is much more potent then Terlipressin as an analgesic agent as shown in Table 1. This difference may be due to the synthetic nature of Terlipressin. It seems that it is less potent because it may have different pharmacokinetic profile. AVP acts through its G protein coupled receptors bound to the adenylate cyclase and phospholipase enzymes [9]. Several studies have shown the analgesic activity of AVP [10,1,3]. Yang *et al* have reported that many AVP containing fibers in the PAG come from PVN neurons, in which high density of endogenous opiate peptide neurons are located. Our results support earlier studies conducted by Amit and Galina [11] who reported that anti-AVP serum was able to attenuate the analgesic effects of AVP as tested by tail clip method.

We used tramadol, a drug which exhibits a modest affinity for µ-opioid and weak affinity for δ and κ opioid receptors [12]. Tramadol also inhibits the re-uptake of noradrenaline and serotonin [13]. Tramadol is normally used for medium intensity short lasting pain. In this study, Tramadol was able to potentiate the effects of AVP and Terlipressin although not very significantly. A similar study done with Tramadol and a different analogue of vasopressin when given in combination showed promise in patients with renal colic [14]. Thus, this study is a novel study which points to the importance of co-administration of Tramadol and vasopressin analogues for possible therapeutic purpose.

References

[1] Yang J.,Y.U.Yan, J.M.Chen, X.T.Xu, W.Y.Liu, and B.C. Lin. 2006. Arginine vasopressin in periaqueductal gray, which relates to anti-nociception comes from hypothalamic paraventricular nucleus in the rat. Neuroscience Letter. 23633, 1-5

[2] Berkowitz B.A and S. Sherman. 1982. Characterization of vasopressin analgesia. J.Pharmacol.Ther.220, 329-334

[3] Tyagi M.G, S. Ramaswamy, D.G. Shewade, and K.D. Tripathi. 1992. Vasopressin acts independently of calcium to induce anti-nociception in mice. Medical Sci. Res. 20 (4), 131-132

[4] Wilsom J, D.J Brackett, L.T.Archer, and L.B. Hinshaw. 1980. Mechanism of impaired cardiac function by vasopressin. Ann. Surg. 191,494-500

[5] Lightman S.L, and M.L Forsling. 1980. Evidence for endogenous opioid control of vasopressin release in man. J. Clin. Endocrinol. Metab. 50:569-571

[6] Rossier J, E Batternberg, Q Pittman, A Bayon, L Kody, R Miller, R Guilleman, and F Bloom. 1979. Hypothalamic enkephalin neurons may regulate the neurohypophysis. Nature (Lond) 277, 653-655

[7] Zimmerman E.A. 1981. The organization of oxytocin and vasopressin pathways in: Martin J.B, S Reichen, K.L Bick (Eds), Neurosecretion and brain peptides, Raven Press, New York, 63-78

[8] Bianchi C, Franceschini, J. 1954. Experimental observation on Haffner's method for testing analgesic drugs. Bri J Pharmacol. 9: 280–284

[9] Jamila Gupte, Gene Cutler, Jin-Long Chen, and Hui Tian. 2004. Elucidation of signaling properties of vasopressin receptor-related receptor 1 by using the chimeric receptor approach. PNAS. 101, 6 1508-1513

[10] Zubrzycka M, and A Janecka. 2005. Effects of centrally administered vasopressin on oro-facial pain perception in rats. Brain Res. 1051, 112-116

[11] Amit Z, Galina ZH. 1988. Stress induced analgesia plays an adaptive role in the organization of behavioral responding. Brain Res Bull.21:955–958.

[12] Raffa R.B, Fridriechs E, Reimann W, Shank R.P, Codd E.E, Vaugh J.L.1992. Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J. Pharmacol. Exp. Ther. 260, 275-285

[13] Driessen B, and Reimann W. 1992. Interaction of the central analgesic, tramadol with the uptake and release of 5-hydroxytryptamine in the rat brain *in vitro*. Br. J. Pharmacol.105, 147-151

[14] Hazhir S, Y A Badr, JN Darabi .2010 .Comparison of intranasal desmopressin and intramuscular tramadol versus pethidine in patients with renal colic. Urol J. Summer.7(3):148-51.