

NEURONAL MECHANISMS OF INCREASED ACCESSIBILITY OF UNPLEASANT MEMORIES IN HELPLESS RATS - A SUMMARY OF PRESENT FINDINGS AND IMPLICATIONS

K.B. KUMAR & K.S. KARANTH

ABSTRACT

Several studies in humans have indicated an association between enhanced retrieval of unpleasant memory and depressive moods. No analogy has so far been demonstrated in laboratory animals, however. A series of experiments, therefore, was initiated in this laboratory with an aim to develop an analogous model of memory bias and to define the neuronal substrate that may account for the differential memory bias, in rats. This paper summarizes current results of these experiments and discusses the likely neuronal mechanism of the enhanced retrieval of unpleasant memories. Also, the implications of these experimental data in understanding the psychobiological aspects of "emotive biasing", so characteristic of human conditions like depression and post-traumatic stress disorders are discussed.

Key words : Depression, learned helplessness, memory bias, DSP-4, p-CPA, CRF, alpha-helical CRF, ACTH, ACTH 4-10, vasopressin, oxytocin.

Recent research into cognitive functioning in clinical depression has suggested, a systematic negative bias in information processing in depressed patients. One aspect of this negative bias is seen in memory experiments. Several studies have indicated that unpleasant memories are more readily retrieved in depressed mood (Breslow et al, 1981; Lloyd & Lishman, 1975; Teasdale & Taylor, 1981) and reverts to normal following a recovery from depression (Forgarty & Hemsley, 1983). This effect of mood has also been demonstrated for nondepressed human volunteers subjected to a variety of mood induction procedures (Natale & Hantas, 1982; Snyder & White, 1983; Teasdale & Russell, 1983). Although available evidence suggests that the depressive mood in humans induces cognitive distortions that increase both the salience and accessibility of unpleasant events (Willner, 1984; 1985), the neurochemical substrates of this cognitive abnormality are yet

to be defined. Also, the retrieval bias that has been seen in depressive moods in humans has so far not been demonstrated in laboratory animals, though an analogous animal model would help in understanding the psychobiological aspects of depressive cognition.

In the past few years, a series of experiments was undertaken in this laboratory to develop an analogous animal model of the cognitive bias seen in depressed patients and to investigate the pharmacological effects of several drugs on appetitive and aversive memory processes. This paper summarizes current results of these experiments and discusses the likely neuronal mechanism of the differential enhancement of unpleasant memory retrieval, so characteristic of human conditions like depression and Post-traumatic Stress Disorder (PTSD) (Mineka & Sutton, 1992; Pitman et al, 1983):

Learned helplessness was first described

K.B. KUMAR & K.S. KARANTH

by Seligman and co-workers within the context of a theory of depression (Seligman et al., 1968). Helplessness is induced by exposing the animals to inescapable stress (usually electroshock), which results in deficits in aversively motivated tasks. In view of the observations that animals exposed to inescapable stress show behaviour in many ways similar to that found in human depression (Overmier & Patterson, 1988) and a wide range of clinically effective antidepressant treatment reverses these behavioral abnormalities (Willner, 1985), learned helplessness model has been regarded as one of the reliable models of human depression (Willner, 1986). Further, several lines of evidence have been advanced recently to suggest that the animal model of inescapable shock serves as a potential model to understand the biological substrates of PTSD in humans (Foa et al., 1992; Southwick et al., 1992). In view of these evidences and the fact that humans who lack control over their stress (induced helplessness) display the same retrieval bias seen in depressive moods (Willner & Neiva, 1986), experiments to define the nature of unpleasant memory, in this series, were conducted in rats subjected to helplessness.

METHOD

Inbred Wistar strain male rats, weighing 320 ± 10 g and maintained in groups of two or three were used in all experiments. The animal colony was housed under standard laboratory conditions on 12-hr light/dark cycle. The training and testing were carried out in the early part of the dark cycle (between 18.30 and 23.30 h), in a sound-attenuated room. The apparatus and methods used in the measurements of behaviour and brain amine levels and drug infusion are described in the relevant research reports. In general, they were standard methods.

RESULTS

Enhanced Retrieval of Unpleasant Memory

In order to define the nature of unpleasant

memory retrieval in the helplessness condition, animals initially exposed to a single unpleasant event in a passive avoidance task were subjected, respectively, to either escapable, inescapable or no shock stress treatments (Kumar & Karanth, 1991). A retention test conducted 48-hr following stress exposure showed an enhanced performance for the passive avoidance task in rats subjected to inescapable shock stress. This improved performance was not observed in escapable or no shock stress groups. These findings suggest an enhanced retrieval of unpleasant memory in rats subjected to inescapable shock within the learned helplessness paradigm. This data is comparable to the qualitative shift that is seen in the retrieval process in clinical depression. This study was repeated in other laboratories employing active and passive avoidance paradigms (Overmier et al., 1994; Pare, 1996) and the findings were replicated.

Differential Enhancement of Unpleasant Memory Retrieval

It was unclear from the previous experiment (Kumar & Karanth, 1991) whether helplessness selectively enhanced the retrieval of unpleasant memories without altering the accessibility of other forms of memory. Therefore, a new paradigm, namely, discriminated approach-avoidance task, for measuring both appetitive and aversive memory processes under identical conditions, was developed (Kumar, 1997), and employed to determine the retrieval bias in the learned helplessness condition (Kumar & Karanth, 1993). Animals were conditioned in a T-maze, initially, to associate the goalboxes with sucrose ingestion and later on, to associate a footshock with one of the goalboxes. Retention of these associations was measured 48-hr after exposure to escapable, inescapable and no shock stress treatments to determine whether exposure to inescapable shock differentially biases retention of appetitive or aversive association. The results showed, an enhanced avoidance behaviour to enter previously shocked goalbox with the absence of such a difference in responding to the nonshocked

NEURONAL MECHANISMS OF UNPLEASANT MEMORY

goalbox by the animals exposed to inescapable footshock stress. This differential response was not observed in two other groups, one given escapable footshock and the other no shock at all. These findings suggest the memory processing is selectively enhanced in helplessness condition and parallels the retrieval bias seen in clinical depression, in negative mood induction procedures and in induced helplessness in humans.

Monoamine Depletion Following Inescapable Footshocks

The effect of footshocks on monoamine, namely, norepinephrine (NE), dopamine (DA) and serotonin (5-HT) levels, in various brain regions was assessed following exposure to escapable, inescapable or no shock stress treatments (Kumar & Karanth, 1998). The concentrations of various amines were assessed either immediately or 48-hr post-stress, by isocratic HPLC (high-performance liquid chromatography) separation method using an electrochemical detector. The results indicated that although depletion of brain amines show time courses, not all stress-induced changes are transient. Inescapable shock stress at 48-hr post-stress interval resulted in significant 14% & 25% reductions of NE in locus coeruleus and hippocampus, respectively, relative to no shock control levels and 16% & 22% reduction, relative to escapable shock control levels. Also, inescapable shock resulted in a significant 27% reduction of 5-HT in brain stem relative to no shock control and 26% reduction relative to escapable shock control levels. No differences were seen between escapable shock and no shock group.

Effects of Central NE and 5-HT Depletion on Memory Retrieval

In the backdrop of the findings from the neurochemical assay that indicated an imbalance of catecholaminergic systems in the brain, particularly NE and 5HT systems, following inescapable footshocks (Kumar & Karanth, 1998), we examined whether an improved retrieval of

unpleasant memory that is seen following inescapable footshocks is also evident after central NE and 5HT depletion (Kumar & Karanth, 1994; 1995a). To this end, the effects of pretest central administration of DSP-4 (N-(2-Chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride), a selective NE neurotoxin and p-CPA (p-Chlorophenylalanine), a selective 5-HT cytotoxin, on memory retrieval in the discriminated approach-avoidance paradigm were assessed.

The results indicated DSP-4 had no effect on open field activities but enhanced latencies to enter both, previously shocked and appetitively reinforced goalboxes. These data thus suggested that central administration of DSP-4 does not result in selective enhanced aversive memories, on the contrary, post-trial NE depletion with DSP-4 neurotoxin might interfere with the retrieval of previously learned association with appetitive stimuli.

Similarly, p-CPA also failed to produce a differential improvement of aversive memory retrieval. On the other hand, p-CPA reduced the latency to enter both, previously shocked and appetitively reinforced, goalboxes. The enhanced traversing behaviour in T-maze, together with an increased central entry in the open field that was observed in depleted animals, could be interpreted, at best, to suggest an anxiolytic activity of p-CPA.

Effects of Stress-responsive Neuromodulators on Memory Retrieval

Several lines of evidence suggest that inescapable footshock is differentially more stressful and the principal effectors of the stress response are pathologically activated in animals subjected to inescapable footshock stress treatment (Dess et al., 1983; Edwards et al., 1990; Harcz et al., 1988). Therefore, we examined whether exogenous neuropeptides or what have been termed "stress-responsive neuromodulators" (Gold, 1988), cause differential memory enhancement and mimic the effect of inescapable footshock on unpleasant memory retrieval (Kumar & Karanth, 1995b; 1995c; 1996; 1997). Forty eight hour after the appetitive and

aversive conditioning, animals were administered one of the neuropeptides prior to testing, to assess the nature of effects on memory for appetitive and aversive stimuli.

The data indicated that systemic administration of adrenocorticotrophic hormone (ACTH) and its fragment ACTH 4-10 (reported to be virtually devoid of adrenocortical activity), central administration of arginine-vasopressin (A-VP) and corticotropin-releasing factor (CRF), when given 20-min before testing, produced a clear cut dissociation between an effect on the memory for unpleasant versus pleasant event. All three peptides when administered before the test selectively enhanced the avoidance response to previously shocked goalbox without altering the approach response to previously nonshocked goalbox. This effect on memory retrieval is similar to that seen following inescapable footshocks (Kumar & Karanth, 1993). Central administration of oxytocin, however, did not produce any significant change in the latencies towards either of the goalbox. CRF antagonist, alpha-helical CRF 9-41 (a-h CRF), when applied centrally 10-min before ICV (intra cerebroventricular) infusion of CRF, antagonized all effects of pretest administration of CRF.

DISCUSSION

This investigation, for the first time, provides evidence that the memory processing is selectively enhanced in the helplessness condition in rats and parallels the retrieval bias that is evidenced in humans in depressive mood and induced helplessness. Longer latencies to enter the goalbox in which a shock was delivered previously, by the helpless rats, together with the absence of any group differences in approaching the other nonshocked goalbox are consistent with the idea that aversive memories are more retrievable following inescapable footshocks.

The lesions of dorsal NE bundle by 6-OHDA (6-hydroxydopamine), though have been reported to impair aversive learning and memory (Crow & Wendlant, 1976; Fibiger &

Mason, 1978), more recent data suggest that NE is critical in acquisition but not in retention of conditioned avoidance behaviour (Bennett & Hock, 1990; Martin & Elgin, 1988). The neurotoxin DSP-4 that selectively depletes NE, has been observed to inhibit spontaneous extinction of conditioned passive avoidance and prevents amnesia development (Loskutova, 1988). Similarly, several studies have shown that selective 5-HT ligands such as 5-HT₂ and 5-HT₃ receptor antagonists enhance passive avoidance behaviour and improve memory retrieval (Chugh et al., 1991; De Noble, 1991). These studies confirm earlier findings of facilitatory actions of p-CPA and electrolytic lesions of the raphe nuclei, in aversive memory tasks (Ogren, 1982). Based on these literature though it could be speculated that NE and 5-HT depletion following inescapable footshocks might have facilitated the retrieval of unpleasant memories in the present investigation, the data with selective NE and 5-HT depletors, do not support this hypothesis. However, it is possible that an alteration in some other neurotransmitter systems, namely, cholinergic (Anisman, 1975), GABAergic (Petty & Sherman, 1981) and opiodergic (Martin et al., 1986), which have been implicated in the learned helplessness phenomenon might have influenced the memory and enhanced the retrieval probability of unpleasant event. The current data do not exclude these possibilities and further work is needed in this direction.

Results from studies that examined the effect of exogenous neuropeptides on memory retrieval produced a clear cut dissociation between an effect on the memory for unpleasant versus pleasant event. ACTH, ACTH 4-10, A-VP and CRF when given before testing primed the retrieval of avoidance response without altering the magnitude of approach response. Alpha-helical CRF, the CRF antagonist, prevented the retrieval enhancing effects of CRF.

The present findings are consistent with the belief that the beneficial effects of neuropeptides on memory are more pronounced with stress-related tasks and less so with

NEURONAL MECHANISMS OF UNPLEASANT MEMORY

appetively-motivated tasks (Kovacs & De Wied, 1994; Kovacs et al., 1987). However, to what extent these findings of the neurochemical involvement in cognitive dysfunctions in helplessness condition is applicable in human disorders, requires further empirical studies. Activation of the hypothalamic-pituitary-adrenal (HPA) axis is one of the abnormalities consistently seen in patients suffering from depression (Charlton & Ferrier, 1989). The mechanism of this abnormality is believed to be related to increased hypothalamic secretion of CRF, a major regulator of ACTH and other POMC (pro-opiomelanocortin) derived peptides (Charlton & Ferrier, 1989; Licinio & Gold, 1991). Studies have also suggested an elevation of CRF, similar to that found in depression, in patients with PTSD (Smith et al., 1989). Although data concerning A-VP levels in depression are relatively few, the available evidence indicate plasma A-VP levels in depressed subjects displaying evidence of biochemical hypercortisolemia are elevated (Inder et al., 1997). Further, the number of A-VP expressing neurons in the paraventricular nucleus levels of the hypothalamus has been reported to be increased in postmortem studies of depressed patients (Purba et al., 1996). On the whole, these data suggest several of the stress-responsive modulators are pathologically activated in depression and PTSD. A number of studies have indicated that peptidergic neurons modulate the information processing and influence learning and memory processes (for a review, see Kovacs & De Wied, 1994). If so, whether the "emotive biasing" so characteristic of these conditions (Pitman et al., 1993), involve the principal mediators of the stress response, as endogenous molecules for the modulation of behavioral processes merit investigation. This hypothesis is further supported by the data recently advanced to suggest, the stress-responsive neuromodulators are causally related to the intrusive recollections of traumatic memory in patients with PTSD (Gold, 1988). Further, the animal model of inescapable shock has been observed to have several behavioral

and biochemical parallels with clinical depression and PTSD (Pitman, 1989; Van der Kolk et al., 1985) and has been regarded as one of the most relevant models to understand the psychobiological aspects of these conditions. In view of this and the fact that helplessness contributes to the etiology of human depression (Abramson et al., 1978; Seligman, 1975), it appears beneficial to pursue research in this direction for new avenues in the psychiatric interventions of these conditions. In this context, the present data may provide an experimental basis for the development of more promising therapeutic strategies for these conditions.

ACKNOWLEDGMENTS

We thank Dr. Gopalan Kutty for his comments on an earlier version of this manuscript.

REFERENCES

- Abramson, L.Y., Seligman, M.E.P. & Teasdale (1978) Learned helplessness in humans. Critique and reformation. *Journal of Abnormal Psychology*, 87, 49-75.
- Anisman, H. (1975) Time-dependent variation in aversively motivated behaviours: Non-associative effects of cholinergic and catecholaminergic activity. *Psychological Review*, 82, 359-385.
- Bennett, M.C. & Hock, F.J. (1990) Interaction between catecholaminergic and opioid systems in an active avoidance task. *Behavioral and Neural Biology*, 53, 258-268.
- Breslow, R., Kocsis, J. & Belkin, B. (1981) Contributions of the depressive perspective to memory function in depression. *American Journal of Psychiatry*, 138, 227-230.
- Charlton, B.G. & Ferrier, I.N. (1989) Hypothalmo-pituitary-adrenal axis abnormalities in depression. A review and a Model.

K.B. KUMAR & K.S. KARANTH

Psychological Medicine, 6, 43-50.

142, 232-237.

Chugh, Y. Saha, N., Sankaranarayanan, A. & Sharma, P.L.(1991) Memory enhancing effects of grainsetron (BRL 43694) in a passive avoidance task. *European Journal of Pharmacology*, 203, 121-123.

Crow, T.J. & Wendlant, S.(1976) Impaired acquisition of a passive avoidance response after lesions induced in the locus coeruleus by 6-OH-Dopamine. *Nature*, 259, 42-44.

De Noble, V.J., Schrack, L.M., Reigel, A.L. & De Noble, K.F.(1991) Visual recognition memory in squirrel monkeys: effects of serotonin antagonist on baseline and hypoxia-induced performance deficits. *Pharmacology, Biochemistry and Behaviour*, 39, 991-996.

Dess, N.K., Linwick, D., Patterson, J. Overmier, J.B. & Levine, S.(1983) Immediate and proactive effects of controllability and predictability on plasma cortisol responses to shock in dogs. *Behavioral Neuroscience*, 97, 1005-1016.

Edwards, E. Harkins, K., Wriht, G. & Henn, F. (1990) Effects of bilateral adrenalectomy on the induction of learned helplessness behaviour. *Neuropsychopharmacology*, 3, 109-114.

Fibiger, H.C. & Mason, S.T.(1978) The effects of dorsal bundle injection of 6-hydroxydopamine on avoidance responding rats. *British Journal of Pharmacology*, 64, 601-605.

Foa, E., Zinbarg, R. & Rothbaum, B. (1992) Uncontrollability and unpredictability in post traumatic stress disorder: An animal model. *Psychological Bulletin*, 112, 218-237.

Forgarty, S.J. & Hemsley, D.R.(1983) Depression and the accessibility of memories. A longitudinal study. *British Journal of Psychiatry*,

Gold, P.W.(1988) Stress-responsive neuromodulators. *Biological Psychiatry*, 24, 371-374.

Harcz, J.L., Minor, T.R., Wilkins, J.N. & Zimmerman, E.G.(1988) Learned helplessness: An experimental model of the DST in rats. *Biological Psychiatry*, 23, 388-396.

Inder W.J., Donald, R.A., Prickett, T.C.R., Frampton, C.M., Sullivan, P.F., Mulder, R.T. & Joyce, P.R (1997) Arginine vasopressin is associated with hypercortisolemia and suicide attempts in depression. *Biological Psychiatry*, 42, 744-747.

Kovacs, G.L. & de Wied, D. (1994) Peptidergic modulation of learning and memory processes. *Pharmacological Reviews*, 46, 269-291.

Kovacs, G.L., Szabo, G., Sarnyai, J. & Telegdy, G.(1987) Neurohypophyseal hormones and behaviour. *Progress in Brain Research*, 72, 109-118.

Kumar, K.B.(1997) Discriminated approach-avoidance task - a new paradigm for measuring both appetitive and aversive memory processes under identical test conditions. *Brain Research Protocols*, 1, 263-268.

Kumar, K.B. & Karanth, K.S. (1991) Enhanced retrieval of unpleasant memory in helpless rats. *Biological Psychiatry*, 30, 493-501.

Kumar, K.B. & Karanth, K.S. (1993) Enhanced processing of an aversive memory following inescapable shock in rats. *Biological Psychiatry*, 33, 169-172.

Kumar, K.B. & Karanth, K.S.(1994) Effects of DSP-4-induced depletion of brain norepinephrine on appetitive and aversive memory retrieval. *Indian Journal of Experimental Biology*, 32, 724-728.

NEURONAL MECHANISMS OF UNPLEASANT MEMORY

- Kumar, K.B. & Karanth, K.S. (1995a)** Effects of p-Chlorophenylalanine-induced depletion of brain serotonin on retrieval of appetitive and aversive memories. *Indian Journal of Experimental Biology*, 33, 837-840.
- Kumar, K.B. & Karanth, K.S. (1995b)** Effects of ACTH and ACTH 4-10 on aversive memory retrieval in rats. *Journal of Neural Transmission*, 101, 223-229.
- Kumar, K.B. & Karanth, K.S. (1995c)** Effects of central administration of arginine-vasopressin on aversive memory retrieval. *Brain Research*, 699, 293-296.
- Kumar, K.B. & Karanth, K.S. (1996)** Alpha-helical CRF blocks differential influence of corticotropin releasing factor (CRF) on appetitive and aversive memory retrieval in rats. *Journal of Neural Transmission*, 103, 1117-1126.
- Kumar, K.B. & Karanth, K.S. (1997)** Effects of central administration of oxytocin on appetitive and aversive memory retrieval. *Indian Journal of Clinical Psychology*, 24, 113-116.
- Kumar, K.B. & Karanth, K.S. (1998)** Effects of escapable and inescapable footshocks on monoamine levels in various brain regions in rats. *Indian Journal of Clinical Psychology*, 25, 102-108.
- Licinio, J. & Gold, P.W. (1991)** Role of corticotrophin releasing hormone 41 in depressive illness. *Baillieres Clinics in Endocrinology and Metabolism*, 5, 51-58.
- Lloyd, G.G. & Lishman, W.A. (1975)** Effects of depression on the speed of recall of pleasant and unpleasant experiences. *Psychological Medicine*, 5, 173-180.
- Loskutova, L.V. (1988)** Participation of the central noradrenergic system in the mechanisms of latent inhibition. *Zhurnal Vyshei Nervnoi Deiatelnosh Imeni I.P. Pavlova*, 38, 1113-1118.
- Martin, G.E. & Elgin, R.J. (1988)** Effects of cerebral depletion of norepinephrine on conditioned avoidance responding in Sprague-Dawley and Fischer rats. *Pharmacology Biochemistry and Behaviour*, 30, 137-142.
- Martin, P., Soubrie, P. & Simon, P. (1986)** Noradrenergic and opioid mediation of tricyclic-induced reversal of escape deficits caused by inescapable shock pretreatment in rats. *Psychopharmacology*, 90, 90-94.
- Minaka, S. & Sutton, S.K. (1992)** Cognitive biases and emotional disorders. *Psychological Science*, 3, 65-69.
- Natale, M. & Hantas, M. (1982)** Effect of temporary mood on selective memory about the self. *Journal of Personality and Social Psychology*, 42, 927-934.
- Ogren, S.O. (1982)** Central serotonin neurons and learning in the rat. In: *Biology of Serotonergic Neurotransmission* (Ed.) N.N. Osborne. Oxford: Oxford University press.
- Overmier, J.B. & Murison, R. Taklo, T. & Espelid, R. (1994)** Effects of traumatic stress on defensive burying: An alternative test of the learned helplessness animal model of depression and enhanced retrieval of unpleasant memories. *Biological Psychiatry*, 36, 703-704.
- Overmier, J.B. & Patterson, J. (1988)** Animal models of human psychopathology. In: *Selected models of anxiety, depression and psychosis*, (Eds.) P. Simon, P. Soubrie & D. Wildocher. Basel: Karger.
- Pare, W.P. (1996)** Enhanced retrieval of unpleasant memories influenced by shock controllability, shock sequence and rat strain. *Biological Psychiatry*, 39, 808-813.
- Petty, F. & Sherman, A.D. (1981)** GABAergic modulation of learned helplessness. *Pharmacology, Biochemistry and Behaviour*, 15,

K.B. KUMAR & K.S. KARANTH

567-570.

Pitman, R.K.(1989) Post traumatic stress disorder, hormones and memory. *Biological Psychiatry*, 26, 221-223.

Pitman, R.K., Orr, S.P. & Shalev, A.Y. (1993) Once bitten, twice shy: Beyond the conditioning model of PTSD. *Biological Psychiatry*, 33, 145-146.

Purba, J.S., Hoogendijk, W.J.G. Hofman, M.A. & Swaab, D.F.(1996) Increased number of vasopressin and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. *Archives of General Psychiatry*, 53, 137-143.

Seligman, M.E.P.(1975) Helplessness: On depression, development and death. San Francisco : Freeman.

Seligman, M.E.P., Maier, S.F. & Geer, J. (1968) The alleviation of learned helplessness in the dog. *Journal of Abnormal Psychology*, 73, 256-262.

Smith, M.A., Jonathan, D., Ritchie, J.C., Kudler, H., Lipper, S., Chappell, P. & Nemeroff, C.B.(1989) The corticotropin-releasing hormone test in patients with post traumatic stress disorder. *Biological Psychiatry*, 26, 349-355.

Snyder, M. & White, P.(1983) Moods and memories: Elation, depression and the remembering of events of one's life. *Journal of Personality*, 50, 149-167.

Southwick, S.M., Krystal, J.,

Johnson, D. & Charney, D.S.(1992) Neurobiology of PTSD. Annual review of Psychiatry, Washington: APA Press.

Teasdale, J.D. & Russell, M.L.(1983) Differential effects of induced mood on the recall of positive, negative and neutral words. *British Journal of Clinical Psychology*, 22, 163-172.

Teasdale, J.D. & Taylor, R.(1981) Induced mood and accessibility of memories: An effect of mood state or of mood induction procedure? *British Journal of Clinical Psychology*, 20, 39-48.

Van Der Kolk, B., Greenberg, M., Boyd, H. & Krystal, J.(1985) Inescapable shock, neurotransmitters and addiction to trauma: toward a psychobiology of post traumatic stress disorder. *Biological Psychiatry*, 20, 314-325.

Willner, P.(1984) Cognitive functioning in depression. A review of theory and research. *Psychological Medicine*, 14, 807-823.

Willner, P.(1985) Depression: A psychobiological synthesis, New York : Wiley.

Willner, P.(1986) Validation criteria for animal models of human mental disorders: Learned helplessness as a paradigm case. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 10, 677-690.

Willner, P. & Neiva, J.(1986) Brief exposure to uncontrollable but not to controllable noise biases the retrieval of information from memory. *British Journal of Clinical Psychology*, 25, 93-100.

*K.B.KUMAR**, Associate Professor of Clinical Psychology, Department of Psychiatry, *K.S. KARANTH*, Professor and Head, Department of Pharmacology, Kasturba Medical College, Manipal-576 119, KARNATAKA

* Correspondance