INTRODUCTION
Time is "nature's way of keeping everything from happening all at once" (National Geographic, March 1990). Time keeping (i.e., timing the occurrence of biochemical, physiological and behavioural events) is crucial to organisms because the ability to anticipate predictably recurrent risks and opportunities that occur in the environment will considerably improve their chances of survival (Pittendrigh, 1993). Several specialized time keeping mechanisms have evolved to address the challenges faced by organisms at different time scales (Hinton and Meck, 1997), thus making them a part of the clockwork universe.

In order to associate to events occurring at particular times of day, organisms use their circadian clock. They also have the ability to measure time durations in the range of seconds to hours (ultradian), weeks (circaseptan), months (circatrigintan), and years (circannual) (Swaab et al., 1996; Hinton and Meck, 1997).

The circadian timing system (CTS) consists of three functional components: a pacemaker, input (afferents) to the pacemaker, and output (efferents) from the pacemaker (Moore, 1983). Pacemaker endogenously generates the rhythm which is entrained to the external light/dark (L/D) cycle via the afferents, and efferents impose this entrained rhythm on the rest of the body (Moore, 1993; 1996). Rhythm generation, its entrainment and overt expression in body functions have been investigated using anatomical (Moore and Lenn, 1972; van den Pol, 1980; van den Pol et al., 1992), behavioural (Stephen and Zucker, 1972; Schwartz et al., 1987; Janik and Mrosovsky, 1994), electrophysiological (Green and Gillette, 1982; Kim and Dudek, 1992; van den Pol and Dudek, 1993), neurochemical (van den Pol and Tsujimoto, 1985; Inouye and Shibata, 1994; Inouye, 1996) and molecular biological (Rusak et al., 1990; Rea et al., 1993; Ishida, 1995; Takahashi, 1995) approaches.

In mammals, the suprachiasmatic nucleus (SCN) is the master pacemaker which is responsible for the generation and entrainment of many circadian rhythms. The retinohypothalamic tract (RHT), the geniculo-hypothalamic tract (GHT), and raphe projections are the major afferents (Moore, 1996), which entrain the pacemaker. The RHT and GHT (via the intergeniculate
leaflet of ventral lateral geniculate nucleus) convey direct and indirect photic inputs respectively, and raphe nuclei provide the non-photic serotonergic input (Turek et al., 1995). The photic information is transduced via RHT by glutamate (Glu) and substance P (SP) to vasoactive intestinal peptide (VIP) neurons of SCN (Moore, 1996). The photic entrainment has been reported to be modulated by non-photic inputs (Selim et al., 1993; Rea et al., 1994; Srkalovic et al., 1994; Bradbury et al., 1997). However, the exact modulatory role of the raphe on photic input to the SCN is not yet investigated.

The rhythm generated by the SCN, though an autonomous property of individual ‘clock neurons’ (Welsh et al., 1995; Herzog et al., 1997; Hastings, 1997) is stabilized and averaged into a coherent period by the cellular communication of SCN (van den Pol and Dudek, 1993; Boukskila and Dudek, 1995). The most common mode of intercellular communication in SCN is by Na\(^{+}\) dependent action potentials. The electrical activity of SCN has been shown to be modulated by serotonin (5-HT) and its agonists/antagonists (Rusak et al., 1993; Rea et al., 1994) among other neurotransmitters. Nevertheless, these studies on serotonergic modulation of SCN electrical activity employed direct administration of 5-HT and its agonists/antagonists into SCN, not by manipulating the natural input to the SCN i.e., the raphe.

One of the important rhythms controlled by SCN is the sleep - wakefulness cycle, and the most common clinical manifestation of circadian dysfunction is disturbed sleep which may lead to (or be the consequence of) depression and other psychiatric disorders (Dawson and Armstrong, 1996). According to the circadian phase advance hypothesis, depression is related to the phase advanced position of the circadian oscillator controlling body temperature (Tb) and rapid eye movement (REM) sleep (Wehr and Wirz-Justice, 1981, 1982). Vogel et al. (1980) proposed that REM sleep deprivation improves depression by stimulating a weakened NREM - REM sleep cycle oscillator. Reduced REM latency in depression has been attributed to the increased activity of a REM excitatory cholinergic mechanism, and to the decreased activity of REM inhibitory aminergic mechanism (Duncan, 1996). However, to our knowledge, no attempt has so far been made to study the biochemical changes in the SCN after REMS deprivation.
Therefore, the objectives of this study are:

1 Raphe mediated serotonergic modulation of SCN electrical activity:- Monitoring of SCN multiple unit activity (MUA) following reversible dorsal raphe (DR) inactivation.

2 Modulation of RHT transmitters by dorsal raphe serotonergic system:- Inactivation of dorsal raphe (DR) nucleus and measurement of consequent changes in the levels of RHT transmitters (Glu and SP) and VIP.

3 Influence of REM sleep deprivation on:
   a RHT transmission:- Measurement of glutamate and substance P (RHT transmitters) and VIP after REMS deprivation,
   b SCN monoamines:- Measurement of the monoamines: 5 hydroxytryptophan (5-HTP), 5-HT, and dopamine (DA) along with γ - aminobutyric acid (GABA) in SCN and other relevant structures (DR, and pineal) after REM sleep deprivation.

Thus, this work, carried out at the levels of rhythm entrainment and generation, and overt expression of rhythms, is about the mind’s clock, the clock that times us.

This thesis is organized in the following sections:- (I) Introduction:- Present section; (II) A brief history of time keeping in mammals:- Review of circadian literature with special emphasis on rodent circadian timing system; (III) Modulation of SCN multiple unit activity by dorsal raphe :- A brief review of the related literature, statement of lacunae and objectives; methodology; results; discussion; (IV) Dorsal Raphe modulation of RHT neurotransmitters:- Review of the related literature, statement of lacunae and objectives; methodology; results; discussion; (V) REM sleep and SCN:- Review of the related literature, statement of lacunae and objectives; methodology; results; discussion; (VI) A view of the clock- analysis and synthesis:- Consolidated discussion of the findings from sections (III), (IV) and (V) in the light of related literature and their implications; (VII) Conclusions:- Enumeration of significant findings and their implications.