Effect of Naloxone, A Specific Opioid Inhibitor, on Blood Pressure Fall During Sleep

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SUMMARY The study was designed to investigate the possible role of endogenous opioids in the fall in blood pressure (BP) seen during initial sleep. Seven normal men, ages 20–30 years, were studied for three consecutive nights. Each night, electroencephalogram, chin electromyogram, electrocorticogram, heart rate (all continuously), and blood pressure (every 15 minutes) were recorded. Night 1 was used for orientation. On nights 2 and 3, subjects received, in randomized order, an infusion of naloxone 0.2 mg/kg over 1 minute or volume-matched saline. Blood pressure data from the first 4 hours of non–rapid eye movement sleep were combined. On the placebo night, systolic BP fell from 114.6 ± 6 mm Hg to 103.7 ± 8 mm Hg (± SD) (p < 0.05, Wilcoxon rank-sum test). On the naloxone night, systolic BP did not change. Neither diastolic BP nor heart rate were influenced by naloxone. These data suggest that endogenous opioids could be involved in the fall in systolic BP seen during initial sleep.

BLOOD PRESSURE normally decreases during sleep.1 Systematic studies of hemodynamic changes during specific sleep states and stages have shown that systemic pressure reaches the lowest values during states 3–4 nonrapid eye movement (non-REM) sleep.1–6 While blood pressure is falling, the secretion of hormones changes substantially. Some of these changes, for example, the decrease in ACTH, are independent of sleep. However, the increase in release of growth hormone and prolactin is, like the decrease in blood pressure, sleep-dependent.6–7 It seemed possible that a common neurotransmitter could be mediating these sleep-dependent cardiovascular and neuroendocrine events. Endogenous opioids have been shown to stimulate the release of growth hormone8 and prolactin9 and to lower blood pressure.10 To test the hypothesis that endogenous opioids might be involved in the blood pressure change during initial sleep, naloxone, a specific opioid antagonist, was administered to normal subjects.

Methods

Seven normal men, ages 20–30 years, were studied in the Stanford University Sleep Disorders Center. After clinical evaluation and obtaining of informed consent, approved by the Medical Committee for the Protection of Human Subjects in Research, subjects were requested to spend three consecutive nights in the facility, in apartment-style bedrooms with controlled temperature. Sleep-wake cycles were continuously monitored throughout each night. The following variables were recorded on a Grass model 7 polygraph: electroencephalogram (C1-A2, C4-A1, of the international 10–20-electrode placement system), electrocorticogram, chin electromyogram, ECG lead II and respiration by means of strain gauges and thermistors. Each night, supine blood pressure was recorded from 60 minutes before lights out to the end of sleep using a Roche Arteriosonde model 1216, which was automatically activated every 15 minutes. The Arteriosonde was interfaced with two channels of the Grass polygraph, and blood pressure was represented simultaneously on the tracing with the other variables. The usual bedtime for most of the subjects was 2230–2300, and lights-out time was kept within these limits.

Night 1 was used for subject orientation and habituation, and the data generated were not analyzed to avoid inclusion of abnormally reduced total sleep time due to the so-called first-night effect.11 On nights 2 and 3, just before lights out, subjects received, in random order, either i.v. naloxone, 0.2 mg/kg, or an equal volume of normal saline. The subjects were not aware of the order of injection and none could differentiate between naloxone and placebo. Infusion time was no longer than 4 minutes.

Data Analysis

All results are expressed as mean ± SD. Systolic and diastolic blood pressures and heart rate were analyzed during stages 1–4 of synchronized sleep and during REM sleep. Almost all blood pressure and heart rate recordings were made during sleep stages 2–4, and no significant differences existed for readings between these three sleep stages. Thus, blood pressure and heart rate during stages 2–4 are combined and expressed as “sleep” values for ease of presentation. Those readings in which cuff inflation led to brief arousal from sleep were not analyzed. This led to elimination of a maximum of 20% of readings during the entire monitoring. Typical recordings during cuff inflation are shown in figure 1. Because naloxone has a short duration of action, analysis was confined to data

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FIGURE 1. The absence of sleep arousal during cuff inflation is clearly evident in these two examples of nocturnal polysomnograms taken during (A) stage 3 non-rapid eye movement (REM) sleep and (B) REM sleep. Systolic and diastolic pressures are monitored on the two lower channels. Sleep states are determined from the joint analysis of the electroencephalogram (EEG) electrooculogram (EOG) and digastric electromyogram (EMG). No intrasleep disruption is noted, and inspiration remains quiet and regular.

Blood pressure and heart rate data were studied in two ways. In the first of these methods, placebo and naloxone values were analyzed separately. Mean data before sleep were compared with data during sleep for the seven subjects using the Wilcoxon rank-sum test. The second method of analysis used a linear plot of blood pressure or heart rate vs time from onset of sleep for each subject. The gradient of the least-squares fit of the data was then determined for placebo and naloxone nights, and these gradients were compared for the seven subjects by the Wilcoxon rank-sum test. Values for duration of sleep stages on the different nights were compared using the same non-parametric methods described above.

obtained during the 4 hours after injection of naloxone or placebo.
Results

Blood Pressure

On the placebo night, systolic blood pressure decreased from 114.6 ± 6 mm Hg before sleep to 103.7 ± 8 mm Hg during the first 4 hours of sleep \((p < 0.05)\). On the naloxone night, systolic blood pressure did not change \((112.4 ± 7 \text{ mm Hg before and } 111.2 ± 9 \text{ mm Hg during the same initial sleep period})\). The pre-sleep pressures were not statistically different on the two nights. A more detailed analysis of the data \((\text{fig. 2})\) shows that the very early decrease in pressure was not influenced by naloxone, but the later decrease during the second sleep cycle was prevented. On the placebo night the mean gradient of least-squares lines for the period 0–4 hours was -2.6 mm Hg/hr. On the naloxone night the mean gradient was 2.8 mm Hg/hr. These results are different at the \(p = 0.01\) level. The relation between systolic blood pressure, sleep stage and time on the placebo and naloxone nights is shown for a representative subject in \text{fig. 3}. The diastolic blood pressure did not show any trend on either the placebo or naloxone night.

Heart Rate

On the placebo night, the heart rate decreased from 65 ± 11 beats/min before sleep to 56 ± 2 beats/min during the first 4 hours of sleep. On the night when naloxone was given, the heart rate decreased from 61 ± 10 to 54 ± 4 beats/min during the same initial sleep period. Neither of these changes was statistically significant.

Sleep Stages

No significant changes occurred in the duration of the various sleep stages. REM sleep latency tended to be greater on the naloxone night \((151 ± 68 \text{ minutes compared with } 110 ± 43 \text{ minutes after placebo})\), but the difference was not significant. Similarly, there was a statistically insignificant decrease in total REM sleep after naloxone \((66 ± 27 \text{ minutes compared with } 85.5 ± 35 \text{ minutes with placebo})\).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Systolic blood pressure (BP) during the first 5 hours after injection of naloxone (0.2 mg/kg) or volume-matched placebo. Mean values for seven subjects.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Systolic blood pressure (BP) throughout the night in a typical subject who received naloxone (0.2 mg/kg) on one night and volume-matched placebo on the other. REM = rapid eye movement.}
\end{figure}
Discussion

The role of the central nervous system in the control of blood pressure is expressed with no greater clarity than in the dramatic events accompanying sleep. However, the mechanisms involved in the decrease in blood pressure during sleep are poorly understood. Normal subjects and patients with high blood pressure experience the same percentage decrease in pressure.\(^5\)\(^,\)\(^12\) The immediate physiologic change leading to a decrease in pressure appears to be a fall in peripheral resistance, as two studies have shown that cardiac output is normal in early sleep when blood pressure is falling sharply.\(^5\)\(^,\)\(^13\) In addition, baroreflex sensitivity increases,\(^14\) and the reflex becomes reset\(^5\) during sleep. Limited evidence indicates that the peripheral sympathetic nervous system is not involved in the blood pressure change during sleep. In cats, surgical sympathectomy diminished but did not prevent the sleep-associated decrease in blood pressure.\(^15\) In hypertensive patients, treatment with drugs that decrease sympathetic effect (propranolol, methyldopa and bethanidine) does not alter the pattern of blood pressure changes during sleep.\(^12\) There is a tendency for blood pressure to be lowest during slow-wave (stages 3–4) sleep and for slight elevations of pressure to occur during REM sleep.\(^4\)

The possibility that endogenous opioids might be involved in the blood pressure changes during sleep was manifest for several reasons. First, there is evidence that these substances can influence blood pressure, because synthetic opioid pentapeptides produce hypotension when injected into the cisterna magna of anesthetized dogs.\(^16\) This effect was reversed by naloxone. Second, the nucleus of the tractus solitarius is intimately involved in blood pressure regulation,\(^14\) and this area of the brain has a high concentration of opiate receptors.\(^17\) Third, morphine-like agents facilitate the baroreceptor reflex at the level of the nucleus of the tractus solitarius, and this reflex is also facilitated during sleep. Fourth, prolactin and growth hormone release is increased during the period when blood pressure is decreasing, and the release of both these hormones is stimulated by endogenous opioids.\(^5\)\(^,\)\(^9\)

Because the concentrations of endogenous opioids cannot be measured in human blood, the specific opioid antagonist naloxone was used to investigate the role of these substances in sleep-associated blood pressure changes. We showed that naloxone in the dose of 0.2 mg/kg lowers prolactin concentration in man,\(^18\) and we therefore used the same dose in this study.

As shown both in our laboratory and by others, naloxone administered intravenously at or above this dose does not influence blood pressure. Thus, 10 mg/kg naloxone administered to rats\(^19\) and 0.2 mg/kg to rabbits\(^20\) had no cardiovascular effect. In a preliminary study in seven conscious, healthy men, we found that 0.2 mg/kg of naloxone does not alter blood pressure (Rubin PC, Blaschke TF: unpublished observation).

Overall, systolic blood pressure significantly decreased on the night when placebo was given and did not change on the naloxone night. More specifically, the fall in systolic pressure during the second sleep cycle was prevented (fig. 2). This observation corresponds closely to our finding with prolactin,\(^18\) where the maximum effect of naloxone was seen 180 minutes after injection of the drug. (Overall, after naloxone administration, plasma prolactin concentrations were lower than those after placebo at times 60–240 minutes inclusive.)\(^18\) The normal volunteers were the same in both experimental studies. Two inferences can be drawn from these results. First, naloxone administration at the onset of sleep prevents the decrease in systolic pressure normally seen during the second cycle of deep sleep. Because naloxone is a pure antagonist at opioid receptors, it seems likely that endogenous opioids are involved in this decrease in pressure. Second, the effect of naloxone appears to be delayed, which implies that opioids themselves are acting indirectly on the blood pressure control mechanisms. It would be relevant to assess whether administration of naloxone earlier in the evening prevents the decrease in pressure seen immediately after sleep begins.

The dose of naloxone used in this study is greater than that necessary to reverse the effects of exogenous opiates such as morphine. However, these doses have been required to antagonize the effects of endogenous opioid analogues.\(^10\)\(^,\)\(^20\) Higher doses of naloxone are probably required in these situations because endogenous opioids have a greater affinity for the receptor.

Because the onset of REM sleep was delayed after naloxone, insufficient data are available for a statistical analysis of blood pressure changes during this sleep stage. However, on both study nights systolic pressure tended to rise during REM sleep (fig. 3). This finding is in keeping with observations using intravenous pressure recording during sleep in normal subjects.\(^4\) The prevention of blood pressure decrease by naloxone was not associated with a rebound increase in REM sleep. On the naloxone night, the prevention of blood pressure decrease was not associated with a rebound fall later in the night.

Diastolic pressure did not change significantly on either night. This probably reflects the inability of the Arteriosonde to detect small changes in blood pressure accurately.\(^21\) Because all the subjects had low diastolic pressures (mean 64 mm Hg), only a small change in pressure would be expected. The heart rate decreased on both nights, but the change failed to achieve significance on nonparametric testing.

The trend toward reduction of total REM sleep time with naloxone requires special investigation. Davis et al.\(^22\) did not observe any differences in the sleep of six normal human volunteers, but they gave much larger doses (2 mg) than we did (0.2 mg/kg).

The control of blood pressure in general and the genesis of hypertension in particular are areas of considerable uncertainty. A substantial role for the central nervous system in blood pressure control is strongly suggested by the impressive decrease in blood
pressure during sleep. Studies on the mechanisms by which such major changes in pressure occur are likely to produce considerable benefits in terms of understanding blood pressure control systems in normotensive and hypertensive man. If endogenous opioids are involved in decreasing blood pressure during sleep, the development of synthetic peptides with opioid activity could have exciting implications for the pharmacology of hypertension.

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