

NEUROCRITICAL CARE THROUGH HISTORY

The Ascending Reticular Activating System



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Abstract

Discovery of the ascending reticular activating system (ARAS) can be attributed to work done in research neuroscientist Horace Magoun's laboratory. Before this finding, most scientists would focus on the diencephalon (and anterior midbrain) but not more caudally. Stimulation of the medial bulbar reticular formation in the pontine and midbrain tegmentum resulted disappearance of synchronized discharge and low-voltage fast activity. The effects were mediated by a thalamic projection system. This finding was a dramatic departure from the early philosophers' ascription of the awake soul to the ventricles (Galen), lumbosacral cord (Plato), pineal gland (Descartes), and even from more modern nineteenth- and twentieth-century hypotheses that the corpus striatum or periaqueductal gray matter housed the "seat of awareness." Magoun and his collaborators closed in on its true location in the cephalic brainstem—clinicians and neuropathologists would soon follow.

Keywords: Ascending reticular activating system (ARAS), Brainstem, Localization of consciousness

It is remarkable that illustrations of the brain—then and now—rarely show a brainstem. The “buried” brainstem just did not catch too much attention. For many early anatomists, the medulla was merely an extension of the spinal cord. Moreover, for decades, neuroscientists—and most prominently the phrenologist Gall, who described many brainstem details—saw only motor nuclei and tracts. Scientists were looking elsewhere for the seat of consciousness, and already in 1911, Henry Head and Gordon Holmes were convinced of the central role of the thalamus (Galen's term for the chamber attributed to vision) as well as serving as a center that responds to sensation—either pleasurable or uncomfortable [1]. The fundamental discovery of the prominent role of the brainstem in sleep and coma (among its other vital functions) had to wait until 1930s. For centuries, sleep was seen as part of a de-afferentiation concept, which means that without sensory input, the brain goes to sleep. (There were competing chemical, circulatory, evolutionary, and ontogenetic theories.) This de-afferentiation hypothesis

led Bremer to perform experimental cutting through different levels of the cat's brainstem—his *cerveau isolé* (upper brainstem) and *encéphale isolé* (lower in the brainstem) preparations. *Cerveau isolé* would produce persistent sleep and a continuous pattern of spindles and slow waves on electroencephalogram (EEG). Alternating sleep and awake states occurred in the *encéphale isolé* preparation essentially pointing out there were afferents in the brainstem in some way or another reaching the cortices of the hemispheres [2].

More specifically, the discovery of the ascending reticular activating system (ARAS) is attributed to research neuroscientist Horace Magoun's laboratory at the University of California, Los Angeles, and his collaborators, Giuseppe Moruzzi (Institute of Physiology, University of Pisa) and Jack French, a neurosurgeon from Long Beach. This landmark but largely unintended discovery demonstrating the plausibility of ascending tracts from the brainstem to the cortex via thalamus to spur cortical function changed our thinking about unconsciousness and sleep. Before this finding, most scientists focused on the diencephalon (and anterior midbrain) level but not more caudally. This localization was considered the most plausible after von Economo—when he was studying the encephalitis lethargica epidemic in 1917—demonstrated

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encephalitic lesions or sleep-inducing tumors in that region [3].

This historical vignette draws on Magoun's 1958 Salmon Lecture at the New York Academy of Medicine [4]. Not only did he challenge the early philosophers' ascription of the awake soul to the ventricles (Galen), or pineal gland (Descartes), but he also contested more contemporary hypotheses such as the corpus striatum [5], or the periaqueductal gray [6] while closing in on the true location of the "waking brain" in the cephalic brainstem.

Prelude to Discovery of ARAS

This was an era when many were performing experiments with severed animal brains. Sherrington would cut through the brain—particularly the mid brain—to find the rigidity he named "decerebrate" responses [7]. Lower cuts in the medulla and upper cord caused flaccidity.

Two key discoveries helped investigators in laboratories. First, Berger's discovery of EEG in 1929 [8] and, second, the discovery nearly 10 years later of its response to stimulation (sound, touch) with a generalized "activation pattern" continuing even after withdrawal of the stimulus. When EEG came into the laboratory and made brainwaves recordable, animal studies (i.e., vivisection) led to transection experiments [2, 9].

Stimulating the reticular formation of the bulb and tegmental portion of the pons and midbrain caused a similar response, but the most excitable portion was the ventromedial thalamus and dorsal hypothalamus. This hypothesis led to experimental destruction. Monkeys with lesions in the central cephalic brainstem remained asleep with "stupor waves" on EEG. The comatose monkeys "showed no signs of awareness of their environment, nor were they capable of initiating any voluntary or purposeful movement" [10].

Another important extension of the work was the stimulation of the sciatic nerve and its recording at key locations, demonstrating a somatic, afferent path [10]. Magoun and colleagues also explored neurotransmitters and found both adrenergic and cholinergic components. (Other neurotransmitters—now known to be abundant—had not yet been discovered.)

Most interestingly, Bremer and Terzuolo (and, later, French) found a corticofugal, much less vigorous projection to the reticular formation with afferent inflow from peripheral receptors. Direct excitation of the cortical areas awakened some—but not all—sleeping monkeys [11].

Magoun (with his visiting professor Moruzzi from the University of Pisa, Italy) worked on Bremer's model of "*encéphale isolé*"—a brain preparation on anesthetized cat with cord transected at C1. Magoun's laboratory was interested in extending Sherrington's findings

that decerebration rigidity occurs after cutting through the bulbar reticular formation. Stimulation of the medial bulbar reticular formation in the pontine and midbrain tegmentum resulted in "abolition of synchronized discharge and introduction of low-voltage fast activity in its place." The effects appeared to be mediated by a diffuse thalamic projection system [12]. Similar responses were found when stimulating the thalami. The distribution of the reticular ascending system was further delineated by stimulating different areas and finding that the EEG response did not change following sections of the cerebral peduncles and tectum but did change with lesions in the mesencephalon tegmentum.

These repetitive lesions resulted in reconstruction and distribution of the ascending reticular activating system within the central cone extending into the bulbar reticular formation to the pons and mesencephalic tegmentum into the caudal diencephalon. French's contribution was equally important in visualizing sleep and awakening in monkeys. Implanted electrodes showed a sleepy monkey awakening after stimulation [10]. Extensive injury to the midbrain tegmentum left a deeply comatose animal without any voluntary or purposeful behavior.

More Characterization

The discovery and initial characterization of the waking (and sleeping) brain in the first half of the twentieth century placed the brainstem front and center in the study of consciousness. One of the first demonstrations of a neural substrate of consciousness was presented in 1948 at the America Medical Association in Chicago. Thompson and Nielsen exhibited a panel titled "Area essential to consciousness: Cerebral localization of consciousness as established by neuropathological lesions." They pointed to diencephalic lesions "where the mesencephalon, subthalamus and mesencephalon meet." They concluded that "both the stupor and coma are permanent and irreversible" [13].

Our current understanding is that the ARAS is indeed a poorly delineated structure consisting of a number of axonal fascicles spreading out in many directions caudal to the pons (about midway and down) (Fig. 1) [14]. The ARAS influences autonomic regulation of respiration, heart rate and blood pressure. The rostral portion of the pons (about midway and up) regulates wakefulness. A bilateral lesion of the tegmentum (and, likely, extending into the medial portion of the brainstem) is needed to affect its function. Only very recent technologies, including tractography, can suggest the presence of fine fiber connections, not imaged with conventional magnetic resonance imaging [15, 16]; additional bundles (supporting the redundancy concept in man) have been identified. This surfeit allows the ARAS to support

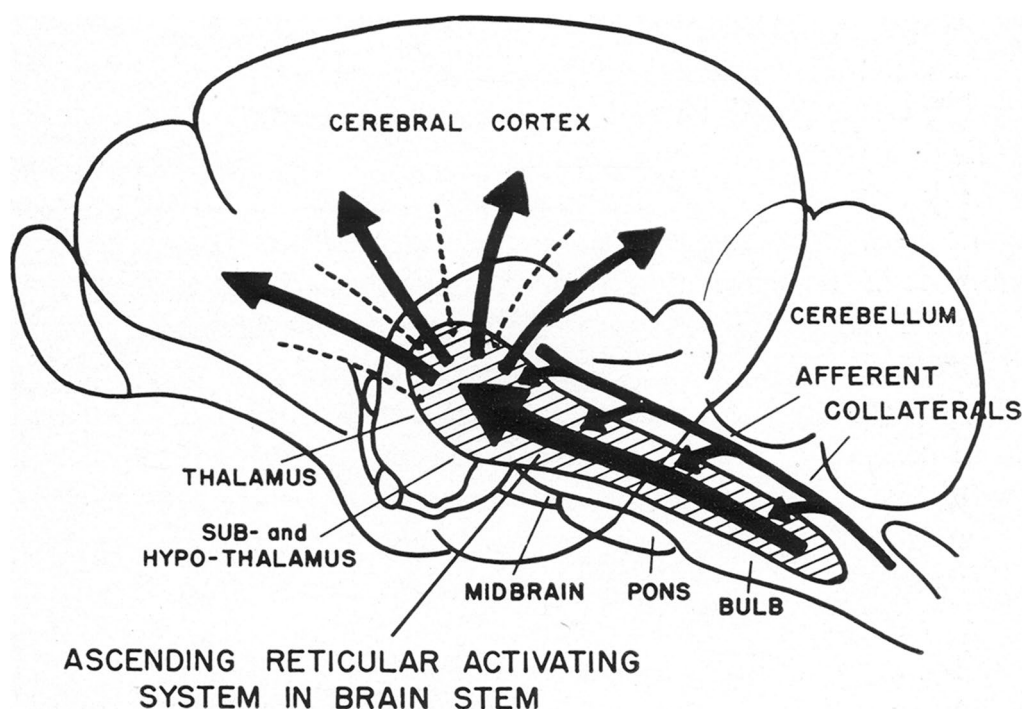


Fig. 1 Conceptual drawing of ARAS (Used with permission from Starzl et al. [14]) used with permission of the publisher (American Physiological Society)

wakefulness unless the entire network is destroyed or fully disconnected from the thalamus [15]. In addition to its location, ARAS controls awakening through the functioning of multiple neurotransmitters such as monoaminergic (noradrenergic, serotonergic, histaminergic) neurons (i.e., locus coeruleus, raphe nuclei, tuberomammillary nucleus) and cholinergic neurons (i.e., pedunclopontine and laterodorsal tegmental nuclei) grouped in the upper brainstem. Some neuronal collections, such as the glutaminergic parabrachial nuclear complex, may be more important than others [17]. While this information may not appear to have direct consequences for the practicing neurointensivist, the burgeoning field of advanced tractography may show destruction in specific areas associated with awareness, which may alter prediction of outcome to include destruction of ARAS as well as supratentorial white-matter injury as determinant factors.

Author Contribution

EFMW researched and wrote the manuscript.

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