viewpoint

5-HT and motor control: a hypothesis

Barry L. Jacobs and Casimir A. Fornal

Barry L. Jacobs and Casimir A. Fornal are in the Program in Neuroscience, Dept of Psychology, Princeton University, Princeton, NJ 08544, USA.

The activity of 5-HT-containing neurons in the brain is activated preferentially in association with motor output in cats. This is especially apparent during changes in muscle tone and during responses mediated by central pattern generators; such as chewing, locomotion and respiration. These and other data support the hypothesis that the primary functions of the 5-HT system in the brain are to facilitate motor output and concurrently inhibit sensory information processing. This hypothesis is applicable phylogenetically, from invertebrates to mammals.

5-HT has been implicated in a bewildering diversity of behavioral and physiological processes[1]. This is not surprising considering the almost ubiquitous distribution of 5-HT-containing axon terminals throughout the CNS[2]. In our own attempts to understand the functional roles of this central neurotransmitter we have taken a tack different from the typical one of manipulating 5-HT and observing which processes are changed. We have studied the electrophysiological activity of brain 5-HT neurons in cats exposed to a variety of behavioral, environmental and physiological conditions. Our results have led to a general hypothesis regarding the behavioral and physiological role of 5-HT in the CNS that accounts for much of the diverse data in this field.

It would appear that the primary function of 5-HT neurons is to facilitate motor output in both the tonic and repetitive modes. In an ancillary manner, the system acts to inhibit sensory information processing, and to coordinate autonomic and neuroendocrine function in relation to changing motor output. Under certain conditions, when the 5-HT system is inactivated, these relationships are reversed: motor output is disfacilitated and sensory information processing is disinhibited.

Distribution of 5-HT terminals

Despite the broad axon-terminal domain of 5-HT neurons, a closer examination reveals a preferential targeting of motor areas in the CNS[2]. For example, in the rat there is a very dense innervation of the ventral horn, the motor nucleus of the trigeminal (MoV), the facial motor nucleus (MoVII), the substantia nigra and the globus pallidus. Another interesting feature of the input to motor areas is its specificity. For example, in the ventral horn of the spinal cord, the 5-HT input preferentially innervates motoneurons projecting to axial rather than distal musculature[2]. In the brainstem of a variety of species there is dense innervation of motoneurons projecting to the large muscles of the jaw, face and neck; by contrast, the more finely controlled extraocular muscles receive sparse 5-HT input[2,3].

If 5-HT neurons in the CNS projected exclusively to motor nuclei, this fact alone would constitute at first sight a strong case for the primacy of motor function for this system. However, there are a multitude of other projections – some quite dense – to non-motor targets such as the hippocampus, the dorsal horn and the dorsal column nuclei (DCN). Although our understanding of the CNS is not yet sufficiently complete to relate structure to function in most cases, we believe that this anatomical pattern is part of the larger picture that interrelates motor outflow to sensory information processing and to autonomic and neuroendocrine regulation. A few examples may help to clarify this point. It is known that 5-HT plays a very important role in the regulation of the theta rhythm in the hippocampus and that this rhythm is often related to different types of motor patterns[4,5]. Although the DCN are primary sensory nuclei, the dense 5-HT input to these sites in cats and monkeys selectively innervates those portions of the nuclei involved in motor function (e.g. projections to the cerebellum, pretectum and the inferior olive) rather than those portions involved in fine somatosensory discrimination (i.e. projections to the ventral posterior lateral nucleus of the thalamus)[6].

Finally, it is worth noting that the organization of 5-HT cell bodies and axon terminals is a primitive one, found in essentially all vertebrate brains, and one that is conserved phylogenetically[7]. (A wide diversity of invertebrate organisms also have 5-HT neurons distributed in various ganglia[7].)

5-HT and behavior

One of the earliest findings regarding 5-HT and behavior came from studies employing its biosynthetic precursors L-5-hydroxytryptophan (5-HTP) or L-tryptophan. When these compounds are administered to any of a variety of mammals, a distinctive and highly reproducible motor syndrome is elicited[8]. Its most conspicuous signs are tremor, rigidity, hindlimb abduction, Straub tail, head shakes or 'wet dog' shakes, lateral head weaving, and reciprocal treading of forepaws. (Similar effects are seen in infra-mammalian vertebrates[8] and humans[9].)

The actions of 5-HT-replacing drugs have also been examined on more discrete aspects of behavior, such as treadmill-induced locomotion in spinal cats[10]. The most prominent action of 5-HT here is to increase the flexor and extensor burst amplitude (a smaller increase is seen in burst duration) during locomotion. In paralysed rabbits, 5-HTP can enhance or even evoke reciprocal flexor and extensor hindlimb nerve activity, with the dominant effect seen in the flexors[11]. We have examined the effects of injecting 5-HT directly into MoV in awake cats, and also observed increases in the amplitude of both the tonic electromyogram (EMG) of the masseter muscle and of an externally elicited jaw-closure (masseteric) reflex[12].

The variety of species in which similar motor effects are seen supports the position that the 5-HT system subserves a common functional role across the vertebrates[8].

Effects on target cells

The effects of 5-HT on motoneurons have been examined in the rat spinal cord and brainstem[13,14]. By itself, 5-HT produces little or no change in neuronal activity. However, when 5-HT is combined with either direct application of excitatory amino acids (e.g. glutamate) or with electrical stimulation of dorsal roots or motor cortex, it produces a strong facilitation of neuronal activity. This effect has been characterized as being bistable, consisting of a 5-HT induced shift from a stable hyperpolarized state, with little or no neuronal activity, to a new stable depolarized 'plateau' state, with tonic neuronal activity[15].

Similar analyses have also been carried out in a more complex situation, where cortical stimulation is used to elicit rhythmic masticatory-like activity in anesthetized guinea pigs[16]. The activity of digastric (jaw opener) motoneurons is directly facilitated by the iontophoretic application of 5-HT, but, as above, only in the presence of glutamate or electrical excitation of these neurons. Additionally, iontophoretic application of 5-HT can facilitate and bring to threshold rhythmic digastric motoneuronal discharges during subthreshold repetitive cortical stimulation. A similar picture is seen when the influence of 5-HT on the neuronal mechanisms mediating fictive locomotion (swimming) is examined in the isolated spinal cord of the lamprey[17]. When applied to the spinal cord or to reticulospinal neurons, 5-HT elicits a depression of the after-hyperpolarization (AHP) that normally follows the action potential. Since the AHP is the primary factor determining frequency regulation, the depression produces an increase in motoneuron discharge. Finally, 5-HT also modulates the intersegmental phase delay in the lamprey spinal cord[18,19].

Basic properties of 5-HT neurons

Over the past 20 years much of the basic neurophysiology of 5-HT neurons in the various raphé nuclei – dorsalis (DRN), medianus (MRN), magnus (NRM) and pallidus (NRPa) (Fig. 1) – has been worked out[20]. The neurons are autoactive, discharging in a stereotyped, almost clock-like manner, with an intrinsic frequency of 1–5 spikes per s (Fig. 2A). The membrane properties that accompany this slow regular activity have been described, as have the ionic currents and channels mediating it.

One of the first important discoveries about these neurons was that this basic pattern of activity was dramatically altered during the sleep–wake–arousal cycle[21,22] (Fig. 2B). From a slow and regular discharge pattern of, for example, 3 spikes per s during quiet waking, activity slows and becomes less regular during slow wave sleep. For the duration of rapid eye movement (REM) sleep, 5-HT neuronal activity falls silent, but in anticipation of awakening, neuronal activity returns to its basal level, or above, several seconds prior to the end of the REM sleep epoch. During an aroused or active waking state, the discharge rate may increase to 4 or 5 spikes per second.
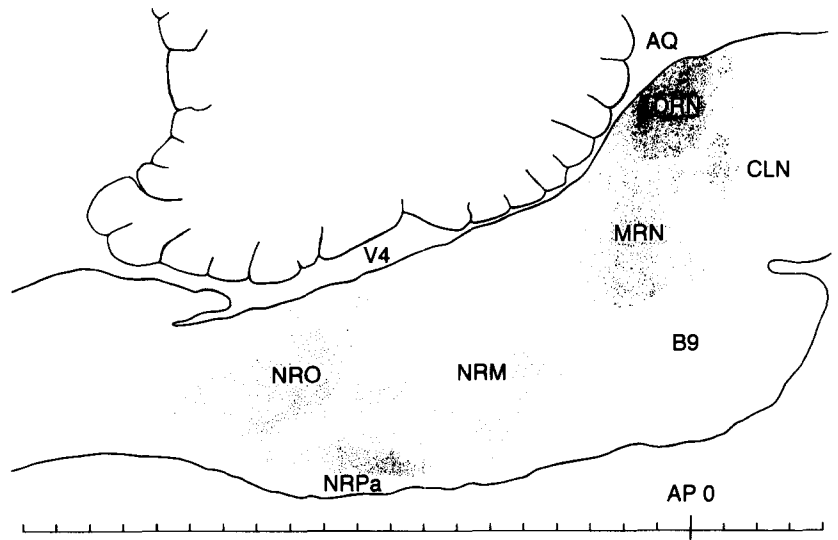

Fig. 1. *Localization of cell bodies of 5-HT-containing neurons in the brainstem of the adult cat. Each dot represents a single 5-HT neuron, as identified histologically through 5-HT immunoreactivity. The figure shows a mid-sagittal section with the 5-HT neurons lying off the midline and collapsed onto this plane. It is important to note that all of the 5-HT perikarya in the cat CNS are localized within the brainstem. This is generally consistent with the hypothesis that these neurons mediate basic physiological and behavioral processes. The cerebellum is at the upper left. Tick marks on the horizontal line at the bottom represent 1 mm demarcations in stereotaxic coordinates. Abbreviations: AP 0, stereotaxic zero; AQ, cerebral aqueduct; B9, a distinct grouping of 5-HT neurons; CLN, central linear nucleus; DRN, dorsal raphé nucleus; MRN, median raphé nucleus; NRM, nucleus raphé magnus; NRO, nucleus raphé obscurus; NRPa, nucleus raphé pallidus. (Taken from Ref. 49.)*

Response of 5-HT neurons to various stimuli

In a series of studies we attempted to determine whether 5-HT neuronal activity was directly related to the physiological (e.g. thermoregulation) or behavioral (e.g. aggression) processes in which it had been implicated. Accordingly, while recording the activity of 5-HT neurons in the DRN, MRN or NRM cats were exposed to the following conditions: a heated environment or a pyrogen[23]; drug-induced increases or decreases in blood pressure[24]; insulin-induced glucoprivation[25]; phasic or tonic painful stimuli[26]; systemic injections of morphine[26]; 100 dB white noise[27]; physical restraint[27]; or a natural enemy (dog)[27].

Despite the fact that most of these stimuli produced strong behavioral responses and physiological changes indicative of sympathetic activation (increased heart rate and blood pressure, and increased levels of plasma catecholamines), none of them significantly activated 5-HT neuronal discharge above that level seen during an undisturbed waking state.

5-HT neuronal activity and motor function

One of the most impressive features of REM sleep is a paralysis mediated by inhibition of motoneurons controlling antigravity muscle tone. Since the activity of 5-HT neurons is also suppressed during REM sleep, it was speculated that there might be a relationship between these two phenomena. Lesions of the dorsomedial pons produce a condition that permits examination of this issue.
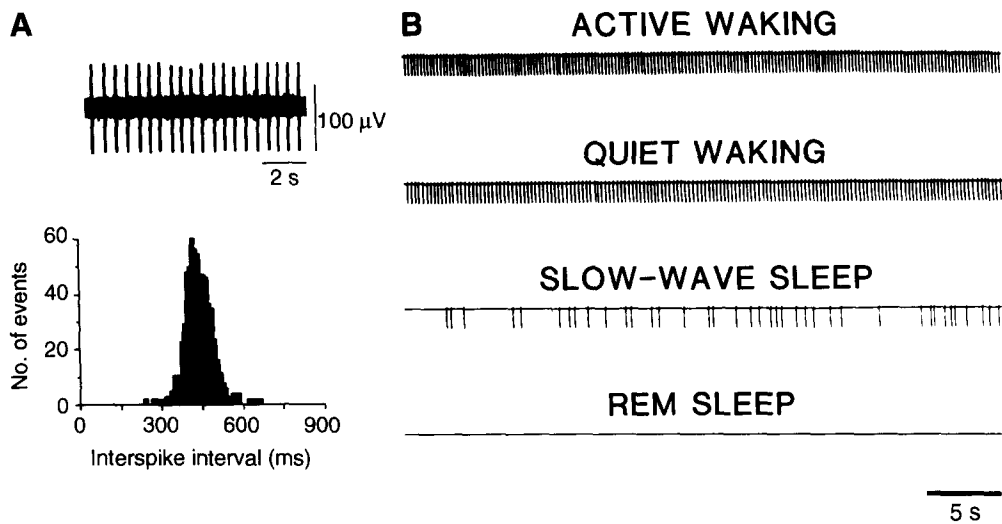
A

100 µV

2 s

60
40
20
0

No. of events

0   300   600   900

Interspike interval (ms)

B

ACTIVE WAKING

QUIET WAKING

SLOW-WAVE SLEEP

REM SLEEP

5 s

Fig. 2. *Activity of a 5-HT-containing neuron from the dorsal raphé nucleus recorded in a freely moving cat. (A) An oscilloscope photograph (top) and a computer-generated interspike interval histogram (bottom), both of which display the near clock-like regularity of discharge of this cell in the awake cat. (B) Polygraph records of the activity of a typical 5-HT-containing neuron in this nucleus during the sleep–wake cycle. Abbreviation: REM, rapid eye movement.*

Cats with this lesion enter a stage of sleep that by all criteria appears to be REM sleep except that antigravity muscle tone is present and the animals are thus capable of movement and even co-ordinated locomotion[28] (Fig. 3A).

During both waking and slow-wave sleep, the activity of 5-HT-containing neurons in the DRN in these pontine-lesioned cats was similar to that of normal animals[29]. However, when these animals entered REM sleep, neuronal activity increased (Fig. 3B). However, those animals displaying the greatest amount of overt behavior and locomotion during REM sleep showed the highest levels of neuronal activity, with some of their 5-HT neurons discharging at a level approximating that of waking.

If the cholinomimetic agent carbachol is microinjected into this same pontine area, a condition somewhat reciprocal to tonic REM sleep can be produced. These animals were awake, as demonstrated by their ability to track stimuli visually, but were otherwise paralysed. However, their DRN 5-HT neurons were inactive[30].

These data suggest that a strong relationship exists between tonic motor activity and 5-HT neuronal discharge. More recently, a relationship has been observed between 5-HT neuronal activity and another type of motor output. When cats engage in a variety of types of oral–buccal activities mediated by central pattern generators (CPGs), such as chewing and biting, licking or grooming with the tongue, approximately a quarter of the 5-HT neurons in the DRN and MRN increase their activity by as much as 2–5 times that observed during quiet waking[20,31] (Figs 4A, B). (The remaining 5-HT neurons simply maintain their state- or tonic motor-related clock-like activity.)

The increased neuronal activity often precedes the onset of the movement by several seconds, but terminates with the offset of the behavior. It is also occasionally phase-locked to the repetitive responses. Some of these neurons are also activated by somatosensory and proprioceptive stimulation of the head and neck area. During a variety of other purposive episodic or phasic movements, even those involving the oral–buccal area, no increase in activity is observed – in fact, a slight decrease is often seen. Under some conditions a dramatic decrease in neuronal activity is observed. For example, if an arousing stimulus such as a loud click elicits an orienting response (indicated by suppression of overt behavior and phasic eye movement towards the source of the sound), 5-HT neuronal activity in the DRN or MRN may fall silent for several seconds[32] (Fig. 4C).

A somewhat complementary picture emerges when an examination is made of the activity of NRPa 5-HT neurons, the primary source of 5-HT to ventral horn motoneurons. These 5-HT neurons are activated (to a level 2–3-fold times that observed during undisturbed waking) in association with repetitive types of behavior mediated by spinal cord

UNIT

EEG

EOG

EMG

10 s

Fig. 3. *Activity of a 5-HT-containing neuron of the dorsal raphé nucleus during an epoch of rapid eye movement (REM) sleep without atonia. The cat raised its head and righted itself during REM sleep. It managed to stand and began to walk. It then began to paw the air. The traces are those of a 5-HT-containing neuron showing minimal activity at the end of slow-wave sleep (as indicated by high-voltage, slow-wave activity in the cortical EEG) and then a virtually complete suppression at the onset of REM sleep. However, with the return of muscle tonus (increased activity in the EMG trace), there is a dramatic increase in unit activity, especially in association with the EMG increases. Abbreviations: EEG, cortical electroencephalogram; EMG, nuchal electromyogram; EOG, electro-oculogram, single unit traces, unpublished observations, B. L. Jacobs, C. W. Metzler, L. E. Ribeiro-do-Valle and C. A. Fornal.*

348

CPGs, such as treadmill locomotion or hyperpnea (induced by exposure to CO_2)[33] (Fig. 5). In some cases there is a strong positive correlation between neuronal activity and speed of locomotion or rate or depth of respiration. Neuronal activity may also increase in association with tonic motor changes such as postural shifts. As with DRN neurons, the activity of NRPa 5-HT neurons is occasionally phase-locked to the repetitive responses (Fig. 5). During the above-mentioned oral–buccal-mediated types of behavior or during other episodic or phasic movements, NRPa 5-HT neurons display little or no increase in activity.

These cellular data from behaving animals have led us to the following conclusions. There is a general relationship between tonic motor activity and 5-HT neuronal activity. Superimposed upon this, in some neurons, is an additional relationship in which a further neuronal activation is seen in association with repetitive CPG-mediated types of behavior. Reciprocally, during the active inhibition of behavior (e.g. during orientation) 5-HT neuronal activity is suppressed. It is also hypothesized that the processing of sensory information is inhibited during tonic and repetitive motor activity and disinhibited during the suppression of motor outflow.

Relationship between motor and sensory processes

There is abundant evidence, in both animals and humans, that sensory transmission is suppressed during gross bodily movements[34,35]. For example, just prior to and during arm movements in the monkey, somatosensory evoked potentials elicited by an irrelevant peripheral stimulus are depressed by as much as 60–70% at the lemniscal, thalamic and cortical levels[35]. A similar mechanism of depressed potentials may explain the well-established involvement of 5-HT in analgesia. As noted above, 5-HT neurons in the NRM are neither activated by a variety of painful stimuli nor by an analgesic dose of morphine[26,36]. It seems that, under physiological conditions, the suppression of nociception by 5-HT at both forebrain and spinal levels occurs as a concomitant result of tonic or repetitive motor outflow. Reciprocally, sensory transmission is enhanced during periods when the activity of 5-HT neurons is suppressed, for example, during orientation. It is well-known that ponto-geniculate-occipital cortex (PGO) waves are inhibited by a tonic release of 5-HT[37], and that these potentials can be evoked by exposing the behaving animal to strong phasic stimuli[38]. Additionally, under pharmacological conditions, when 5-HT neurotransmission is compromised, this disinhibition of sensory processing is manifested as increased responsiveness or enhanced excitability or sensitivity in a variety of paradigms, including nociception[39,40].

In a similar manner, it is hypothesized that 5-HT neurons facilitate the well-known sympathetic activation that accompanies, and even anticipates, motor activity[41]. (For a recent review of the sympathoexcitatory effects of 5-HT in the intermediolateral column of the spinal cord, see Ref. 42.) In this context, it should be recalled – as described
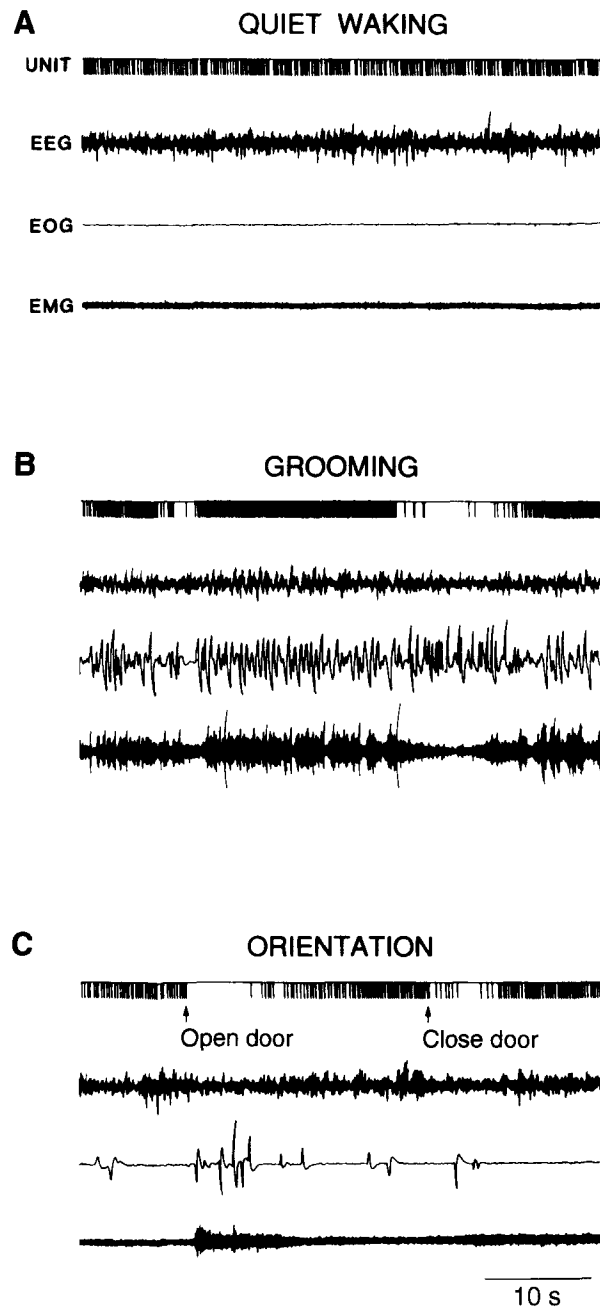

A QUIET WAKING

UNIT

EEG

EOG

EMG

B GROOMING

C ORIENTATION

Open door   Close door

10 s

Fig. 4. Polygraph records from a cat displaying the activity of a 5-HT-containing neuron from the dorsal raphé nucleus during different types of behavior. (A) The distinctive slow and regular activity of 5-HT-containing neurons typically observed during quiet waking. (B) Strong activation (2–5 times greater than during quiet waking) of neuronal activity during oral–buccal-related grooming of the body. Note that in the several instances when there is a pause in grooming, as reflected in the change in the EMG trace, neuronal activity dramatically slows. (C) Neuronal activity may fall silent when the animal is exposed to a strong stimulus that causes an orienting response. In this case, the door to the room housing the recording chamber was opened and then closed approximately 25 s later. Note the phasic eye movement and increased EMG activity coincident with the initial orientation. Abbreviations: EEG, cortical electroencephalogram; EMG, nuchal electromyogram; EOG, electroculogram. [Part (C) taken from Ref. 24.]
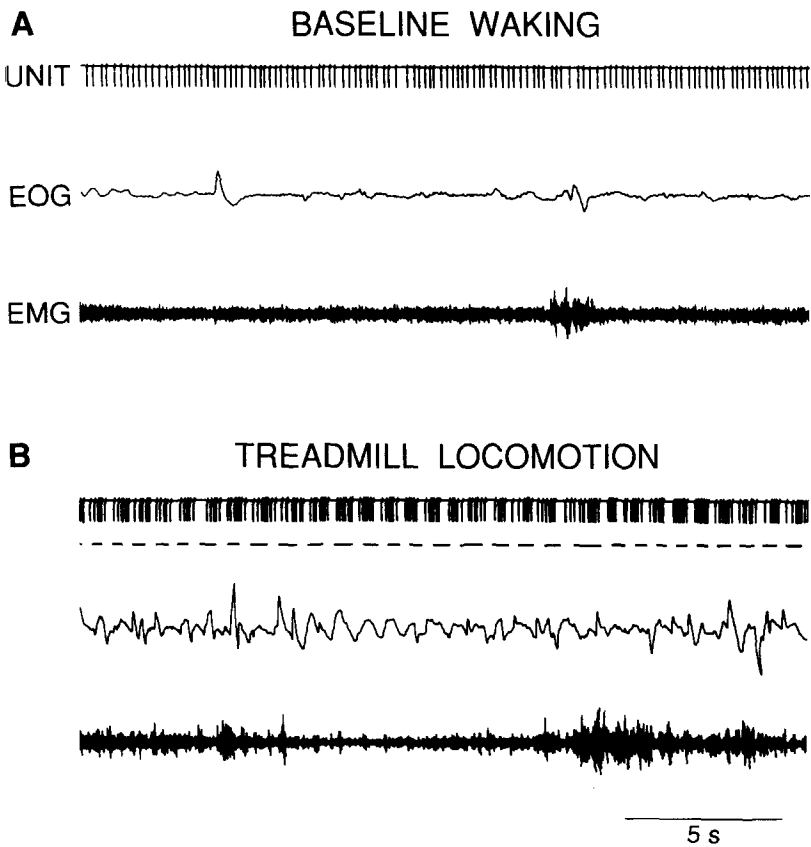
A   **BASELINE WAKING**

UNIT ⲧⲧ

EOG ∿∿∿∿⌒⌒⌒⌒⌒⌒⌒⌒

EMG ▰▰▰▰▰▰▰▰▰▰▰▰▰▰▰

B   **TREADMILL LOCOMOTION**

|||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||

- -

⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊⩊

▰▰▰▰▰▰▰▰▰▰▰▰▰▰▰

_____5 s_____

Fig. 5. *Polygraph records from a cat displaying 5-HT neuronal activity in the nucleus raphé pallidus during different types of behavior.* **(A)** *Neuronal activity during undisturbed waking with a few small movements, as reflected in the electroculogram (EOG) and nuchal electromyogram (EMG) traces.* **(B)** *Activity of the same cell during locomotion on a treadmill (at a speed of approximately 0.6 ms^{-1}). The overall level of neuronal activity increased during locomotion by approximately twice as much compared with neuronal activity, during undisturbed waking. Also, the pattern of neuronal activity changed from a clock-like one to one associated with the phase of the gait (each complete stepping cycle is indicated by the thick black lines below the unit trace). Abbreviation: EEG, cortical electroencephalogram.*

above – that 5-HT neuronal activation often precedes increases in motor activity or muscle tone.

5-HT in invertebrates

Studies of 5-HT function in invertebrates provide striking parallels to many aspects of the data from vertebrates described in this review. This is impressive, in view of the enormous differences in their gross bodily morphology, ecological niche (terrestrial rather than aquatic for the invertebrates in these studies) and general organizational pattern of their nervous systems (a brain rather than nervous ganglia). Several examples will help to make this point. (1) Direct injection of 5-HT into the systemic circulation of several arthropods results in a general motoric change that may be described as overall flexion[43,44]. (2) When they have been examined (e.g. in lobsters) 5-HT neurons are found to be endogenously active[44]; in both lobsters and *Aplysia* 5-HT neurons discharge with a slow and regular pattern (0.5–1.0 Hz) that can increase to 2–5 Hz during feeding or with postural changes[44,45]. Furthermore, in *Aplysia* the 5-HT metacerebral cell

alters its somewhat regular firing pattern to become phase-locked to oral–buccal movements during feeding[45]. (3) In several molluscs, arthropods and annelids, 5-HT modulates rather than mediates motor outflow – often by acting on CPG[46]. The involvement in motor control appears to be with both tonic (e.g. posture)[43] and repetitive (e.g. swimming or biting) outputs[46,47]. (4) In *Aplysia* and leeches, 5-HT exerts its effects on behavior at multiple levels (e.g. directly on muscles, on CPGs and on the cardiovascular system)[45,48].

Concluding remarks

During an undisturbed waking state, brain 5-HT neurons discharge with a slow and regular firing that is a manifestation of their intrinsic activity. This regular firing during waking creates a steady synaptic release of 5-HT, which provides a tonic influence that modulates motor-system neuronal activity.
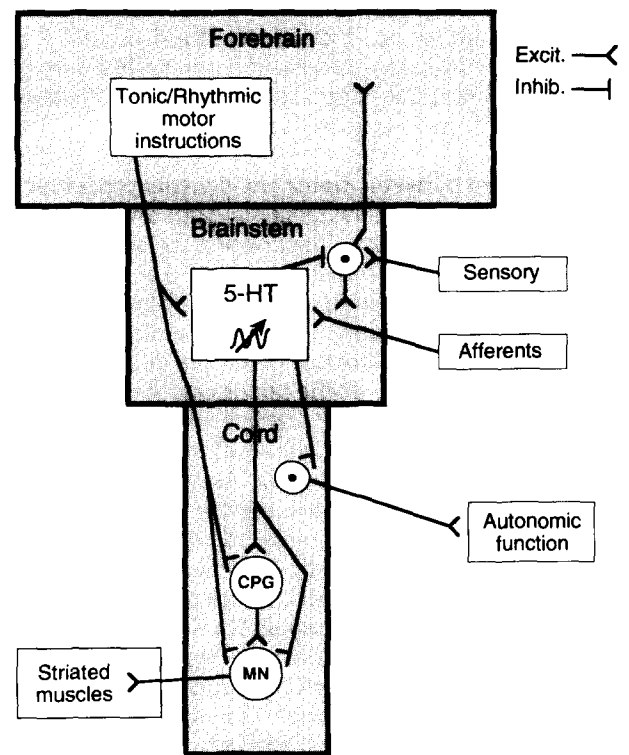

Fig. 6. *The major components of the motor hypothesis of 5-HT function. When voluntary tonic or rhythmic motor outflow is initiated, forebrain motor commands are simultaneously sent to α motoneurons (MN) brainstem or spinal cord central pattern generators, and to brain-stem 5-HT neurons. The output of 5-HT neurons serves several functions simultaneously; facilitates central pattern generator and α motoneuron activity; orchestrates autonomic and neuroendocrine (not shown) output with motor outflow; and inhibits sensory information processing. 5-HT neurons are shown to be driven by an endogenous oscillator (sine wave with arrow) and to be phasically activated by various afferents. Not shown is the possibility that different groups of 5-HT neurons may facilitate different motor functions; for example, neurons in the nucleus raphé pallidus affecting respiration or neurons in the dorsal raphé nucleus affecting oral–buccal movements.*

During gross repetitive types of motor behavior that are mediated by brainstem and spinal cord CPGs, subpopulations of 5-HT neurons are co-activated, attaining discharge levels several times greater than that observed during undisturbed waking. This activation, seen in association with, for example, chewing, grooming or running, is sometimes phase-locked to the cyclic motor output. It is also interesting to note that the distribution of 5-HT axon terminals in the spinal cord and brainstem is consistent with the involvement of 5-HT in patterned movement employing gross skeletal muscles rather than those movements using finer or more discrete muscles (Fig. 6). Thus, in the spinal cord there is a denser input to the medial portion of the ventral horn, where axial motoneurons serving the trunk and limbs are found, compared with the lateral portions, where distal motoneurons serving paws and digits are found. Similarly, in the brainstem, there is a much denser 5-HT input to MoV and MoVII, controlling jaw and facial muscles, respectively, compared with the nuclei controlling fine eye movements.

Several important functions may be served by these 5-HT inputs. They may smooth motor outputs, and also obviate the need for continuous repetitive excitatory inputs to maintain a continuous output in motor systems. By augmenting weak or polysynaptic inputs, 5-HT may also bring motoneurons to threshold. The anticipation of motor activity by 5-HT neurons suggests that they may serve a priming function for motor output. 5-HT may also serve a timing or integrative function, such as that observed in the intersegmental delay in the spinal cord of the lamprey. The simultaneous inhibition of 'irrelevant' sensory information processing acts to suppress inputs that might disrupt motor output (Fig. 6). Conversely, when phasic 5-HT neuronal activity is decreased (e.g. during orientation) it serves to sharpen sensory function while disfacilitating motor output and thereby preventing it from disrupting sensory processing. Finally, the involvement of 5-HT in autonomic and neuroendocrine regulation serves a support function for motor output, such as increased blood flow to skeletal muscles, or increased carbohydrate consumption for maintaining a stable glucose supply to the brain.

The apparent commonality of these results broadly across the animal kingdom is striking. Unfortunately, sufficiently detailed data are not available to establish whether there are phylogenetic trends in this relationship. It is suggested tentatively that 5-HT serves an integrative overarching function, rather than being discretely and separately involved in the great diversity of behavioral and physiological processes in which it has been implicated.

Selected references

1 Whitaker-Azmitia, P. M. and Peroutka, S. J. (1990) *The Neuropharmacology of Serotonin*, New York Academy of Sciences
2 Steinbusch, H. W. M. (1981) *Neuroscience* 4, 557–618
3 Takeuchi, Y., Kojima, M., Matsuura, T. and Sano, Y. (1983) *Anat. Embryol.* 167, 321–333
4 Vanderwolf, C. H., Baker, G. B. and Dickson, C. (1990) in *The Neuropharmacology of Serotonin* (Whitaker-Azmitia, P. M. and Peroutka, S. J., eds), pp. 366–382, New York Academy of Sciences
5 Marrosu, F., Fornal, C. A., Tada, K., Metzler, C. W. and Jacobs, B. L. (1991) *Soc. Neurosci. Abstr.* 17, 1437
6 Blomqvist, A. and Broman, J. (1993) *J. Comp. Neurol.* 327, 584–596
7 Parent, A. (1981) in *Serotonin Neurotransmission and Behavior* (Jacobs, B.L. and Gelperin, A., eds), pp. 3–34, MIT Press
8 Jacobs, B. L. (1976) *Life Sci.* 19, 777–785
9 Sternbach, H. (1991) *Am. J. Psychiatry* 48, 705–713
10 Barbeau, H. and Rossignol, S. (1991) *Brain Res.* 546, 250–260
11 Viala, D. and Buser, P. (1969) *Brain Res.* 12, 437–443
12 Ribeiro-do-Valle, L. E., Metzler, C. W. and Jacobs, B. L. (1991) *Brain Res.* 550, 197–204
13 McCall, R. B. and Aghajanian, G. K. (1979) *Brain Res.* 169, 11–27
14 White, S. R. and Neuman, R. S. (1980) *Brain Res.* 188, 119–127
15 Hultborn, H. and Kiehn, O. (1992) *Curr. Opin. Neurobiol.* 2, 770–775
16 Katakura, N. and Chandler, S. H. (1990) *J. Neurophysiol.* 63, 356–369
17 Grillner, S., Wallen, P. and Brodin, L. (1991) *Annu. Rev. Neurosci.* 14, 169–199
18 Harris-Warrick, R. M. and Cohen, A. H. (1985) *J. Exp. Biol.* 116, 27–46
19 Matsushima, T. and Grillner, S. (1992) *J. Neurophysiol.* 67, 1683–1690
20 Jacobs, B. L. and Azmitia, E.C. (1992) *Physiol. Rev.* 72, 165–229
21 McGinty, D. J. and Harper, R. M. (1976) *Brain Res.* 101, 569–575
22 Jacobs, B. L. and Fornal, C. A. (1991) *Pharmacol. Rev.* 43, 563–578
23 Fornal, C. A., Litto, W. J., Morilak, D. A. and Jacobs, B. L. (1987) *Exp. Neurol.* 98, 388–403
24 Fornal, C. A., Litto, W. J., Morilak, D. A. and Jacobs, B. L. (1990) *Am. J. Physiol.* 259, 963–972
25 Fornal, C. A., Litto, W. J., Morilak, D. A. and Jacobs, B. L. (1989) *Am. J. Physiol.* 257, 1345-1353
26 Auerbach, S., Fornal, C. and Jacobs, B. L. (1985) *Exp. Neurol.* 88, 609–628
27 Wilkinson, L. O. and Jacobs, B. L. (1988) *Exp. Neurol.* 101, 445–457
28 Morrison, A. R. (1979) in *Psychobiology and Physiological Psychology* (Vol. 8) (Sprague, J. M. and Epstein, A. N., eds), pp. 91–131, Academic Press
29 Trulson, M. E., Jacobs, B. L. and Morrison, A. R. (1981) *Brain Res.* 226, 75–91
30 Steinfels, G. F., Heym, J., Strecker, R. E. and Jacobs, B. L. (1983) *Brain Res.* 279, 77–84
31 Ribeiro-do-Valle, L. E., Fornal, C. A., Litto, W. J. and Jacobs, B. L. (1989) *Soc. Neurosci. Abstr.* 15, 1283
32 Jacobs, B. L., Metzler, C. W., Ribiero-do-Valle, L. E. and Fornal, C. A. *Soc. Neurosci. Abstr.* (in press)
33 Veasey, S. C., Fornal, C. A., Metzler, C. W., Milman, W. and Jacobs, B. L. *Soc. Neurosci. Abstr.* (in press)
34 Chapin, J. K. (1987) in *Higher Brain Functions: Recent Explorations of the Brain's Emergent Properties* (Wise, S. P., ed.), pp. 181–209, Wiley & Sons
35 Chapman, C. E., Jiang, W. and Lamarre, Y. (1989) *Exp. Brain Res.* 72, 316–334
36 Potrebic, S., Fields, H. L. and Mason, P. (1992) *Soc. Neurosci. Abstr.* 18, 683
37 Ruch-Monachon, M. A., Jalfre, M. and Haefely, W. (1976) *Arch. Int. Pharmacol. Ther.* 219, 269–286
38 Bowker, R. M. and Morrison, A. R. (1976) *Brain Res.* 102, 185–190
39 Wilkinson, L. O. and Dourish, C. T. (1991) in *Serotonin Receptor Subtypes: Basic and Clinical Aspects* (Peroutka, S. J., ed), pp. 147–210, Wiley-Liss
40 LeBars, D. (1988) in *Neuronal Serotonin* (Osborne, N.N. and

Hamon, M., eds), pp. 171–229, Wiley & Sons
41 Guyton, A. C. (1981) *Textbook of Medical Physiology* (6th edn), pp. 344–346, W. B. Saunders
42 McCall, R. B. and Clement, M. E. (1989) *Brain Res.* 477, 172–182
43 Kravitz, E. A. (1988) *Science* 241, 1775–1781
44 Ma, P. M., Beltz, B. S. and Kravitz, E. A. (1992) *J. Neurophysiol.* 68, 36–54
45 Kupfermann, I. and Weiss, K. R. (1981) in *Serotonin Neurotransmission and Behavior* (Jacobs, B. L. and Gelperin,

A., eds), pp. 255–287, MIT Press
46 Harris-Warrick, R. M. (1988) in *Neural Control of Rhythmic Movements in Vertebrates* (Cohen, A. H., ed.), pp. 285–331, Wiley & Sons
47 Nusbaum, M. P. and Kristan, W. B. (1986) *J. Exp. Biol.* 122, 277–302
48 Lent, C. M. (1985) *Brain Res. Bull.* 14, 643–655
49 Jacobs, B. L. (1987) in *Progress in Psychobiology and Physiological Psychology* (Vol. 12) (Epstein, A. N. and Morrison, A. R., eds), pp. 171–206, Academic Press

letter to the editor

Aged dogs, space (and scissors)

It has been pointed out (Terry, R., pers. commun.) that my review[1] on neuron atrophy during aging contains an error and several omissions of primary references.

In Table I on age-related changes in the brains of various species, I indicated wrongly that the aged dog lacks senile plaques with βA4 amyloid. There is agreement that senile plaques are infrequently stained in aging dogs by Bielschowsky's stain, a standard stain for senile plaques in humans[2,3]. However, immuno-cytochemistry using monoclonal antibodies to βA4 epitopes has shown that βA4-containing plaques are ubiquitous in dogs aged 220 months or older[2].

Incomplete referencing in Table I and the use of secondary sources in preference to large numbers of primary papers were a consequence of editorial 'scissors' that limited the number of references. With this policy, *TINS* keeps good company with increasing numbers of publications. Such parsimony spares space that may allow more individual articles to be published. However it also inhibits the emergence of subjects like that of my article, in which insights come from scattered articles that may not be cited widely or reviewed often.

Caleb E. Finch
University of Southern California, Los Angeles, CA 90089-0191, USA.

References
1 Finch, C. E. (1993) *Trends Neurosci.* 16, 104–110
2 Wiesnewski, H. *et al.* (1990) in *Alzheimer's Disease: Epidemiology, Neuropathology, Neurochemistry, and Clinics* (Maurer, K. *et al.*, eds), pp. 151–168, Springer-Verlag
3 Ball, M. *et al.* (1983) *Neurobiol. Aging* 4, 127–131

TINS Editorial Policy

Trends in Neurosciences is the leading neuroscience review journal, publishing timely and wide-ranging feature articles enabling neuroscientists to keep up to date in and around their own fields.

Reviews form the foundations of each issue and offer concise and authoritative summaries of important areas of neuroscientific research; *Research News* describe recent developments within a particular field; *Perspectives* discuss areas of historical, social and more oblique interest – offering interesting insights into current research; *Viewpoints* include more controversial or synthetic ideas. The new *Debate* section offers a series of alternative viewpoints on a currently hotly debated topic. *Perspectives on Disease* discuss how basic neurobiological research can be applied to neurological disease; *Techniques* offers a guide to new methods and their use.

Articles in *TINS* are usually commissioned by the Editor, in consultation with the Editorial Board. All are subject to peer and editorial review – commissioning does not guarantee publication.