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RESEARCH ARTICLE

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Neuronal responses to 5-hydroxytryptamine in the red nucleus of rats

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Abstract The effects of microiontophoretic 5-hydroxytryptamine (5-HT) on the firing rate of red nucleus (RN) neurons were studied in urethane-anesthetized rats. The background discharge rate of almost all the neurons tested (97%) was modified by 5-HT, and generally increased (89%). Responses were dose dependent. Twenty-three percent of the excitatory responses were preceded by a short inhibitory phase. No significant difference in the effect of 5-HT was found between those RN neurons that project to the spinal cord and those that do not. The excitatory responses to 5-HT were blocked or greatly reduced by the 5-HT antagonists methysergide and ketanserin, and were even reversed in some cases. The 5-HT_2/5-HT_{1A} antagonist spiperone, in small doses, also blocked the transient inhibitory phases in addition to the excitatory effects. In RN neurons exhibiting a short-lasting inhibition in the response to 5-HT, the 5-HT_{1A} agonist 8-hydroxy-2(di-*n*-propyl-amino)tetralin (8-OH-DPAT) induced inhibitory effects. These results support the hypothesis that 5-HT exerts control throughout the RN, mostly by acting on 5-HT_2 receptors. Furthermore, an influence of this amine on the electrical activity of small groups of RN neurons by 5-HT_{1A} receptors, and eventually by different mechanisms, appears probable. The functional significance of serotoninergic control of RN neuronal activity is discussed.

Key words Red nucleus · 5-Hydroxytryptamine · 5-HT receptors · Microiontophoresis · Rat

Introduction

The function of the mesencephalic red nucleus (RN) in the context of motor control is to process information from motor cortex and cerebellar nuclei, both delivering it to the spinal cord via the rubrospinal tract (RST) and relaying it to the cerebellum via the rubro-olivary pathway (Massion 1967; Martin and Ghez 1988). The neurotransmitters involved in mediating this type of information in the RN are glutamate, acetylcholine and, at least with regard to interneurons, γ-aminobutyric acid (GABA) (Neioullon et al. 1988). The RN, although traditionally classified as a motor structure, receives some afferents which are related to nociception rather than movement (Matsumoto and Walker 1991) and some which contain serotonin (5-HT) rather than classical neurotransmitters (Pierce et al. 1976; Bernays et al. 1988).

Biogenic amines, and specifically 5-HT, are known to influence the electrical neuronal activity of motor structures (McCall and Aghajanian 1979; Strahlendorf et al. 1984; Gardette et al. 1987; Hicks et al. 1989; Takahashi and Berger 1990; Licata et al. 1990). A hypothesis recently advanced suggests that the primary function of 5-HT in the central nervous system is to exert a generalized facilitatory influence on motor output (Jacobs and Fornal 1993). In this context we found it useful to establish whether, and to what extent, 5-HT is able to modify neuronal firing in the RN in the rat. Our subordinate goal was to verify whether, in this regard, the behavior of RN neurons that project to the spinal cord was the same as that of those that do not. Preliminary reports have been presented elsewhere (Licata et al. 1993b).

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Methods

The experiments were performed on male Wistar rats anesthetized with urethane (1.5 g/kg intraperitoneally). *Principles of laboratory animal care* (NIH publication no. 86–23, revised 1985) was followed as well as current Italian law regarding the protection of animals.

The temperature of the animal was maintained with a heating pad and the heart rate was monitored continuously during the experiment. Supplementary doses of intraperitoneal anesthetic were administered whenever the heart rate exceeded 370–380 beats min^{-1}. Exposed tissue was covered with a gel of agar-agar (2%) to prevent desiccation.

The rats were kept in the prone position and the head held within a stereotaxic frame. Small holes were drilled in the surface of the skull at coordinates corresponding to the RN and RST (Paxinos and Watson 1986). Action potentials from single RN

neurons were recorded extracellularly through a barrel of a five-barrel glass micropipette (resistance 7–12 MΩ) containing a 4% solution of Pontamine Sky Blue in 3 M NaCl. A recording was rated as neuronal activity if the spike amplitude was at least 4 times greater than the noise level and remained unmodified during the tests.

Single unit activity was tested for an antidromic response to stimulation of the RST (P, 1.3–2.3; L, 2.9–3.1; V, 0–0.2). Stimuli (intensity 20–100 μA, duration 20–50 μs) were applied to the RST by a steel electrode insulated except at the tip (resistance 0.5–1.0 MΩ). We verified that responses were able to follow a stimulation frequency up to 500 Hz and that the spontaneous and the antidromic spike collided.

Each of three barrels of the micropipette was filled with one of the following solutions: 5-HT (Sigma, 30 mM, pH 4.5), methysergide bimaleate (Sandoz, 10 mM, pH 4.5–5.0), ketanserin tartrate (Janssen, 10 mM, pH 4.5), 8-hydroxy-2(di-n-propyl-amino)tetralin (8-OH-DPAT, Sigma, 20 mM, pH 4.5–5.0), spiperone (Sigma, 2μM, pH 5), sodium-l-glutamate (Sigma, 100 mM, pH 8). All drugs were made up in distilled water with the exception of 5-HT, which was dissolved in 165 mM NaCl. A barrel filled with 3 M NaCl enabled an automatic current balancing circuit to neutralize any voltage shift due to currents close to the neuron. Retaining currents of 5–20 nA (negative for all drugs except glutamate) were applied to the barrels to reduce drug diffusion during electrode penetrations. Although the microiontophoresis device had a balancing system, positive or negative currents were regularly applied, as a control, through the barrel filled with 3 M NaCl (balance) to verify that these currents did not influence neuronal firing rates. Whenever such a current ejection induced variations of more than the standard deviation of the mean firing rate, the unit was excluded from further analysis. Drugs were ejected using microiontophoretic pulses of 30–60 s duration at various current steps. Ejection currents were positive for 5-HT and 8-OH-DPAT and negative for glutamate. 5-HT antagonists (methysergide, ketanserin, spiperone) were applied for periods of 4–20 min. The interval between two 5-HT applications was not standardized; instead we waited for the firing rate to return to the initial value and then ejected the drug after a delay of 1–2 min.

Amplified action potentials from a single cell were recorded and processed by a personal computer provided with a peripheral device for acquiring signals (1401-CED, Cambridge, UK) and the appropriate software (Spike2, CED).

The number of spikes in successive 1 s epochs was calculated on-line and plotted graphically by a rate meter with 5 s bins. The 180 data, referred to 3 min of spontaneous activity, were used to calculate the mean firing rate (and the standard deviation, SD). This value was defined as the mean background activity and used in the off-line statistics. If the SD exceeded 20% of the mean background activity, the unit was classified as unstable and excluded from further analyses. In contrast, whenever the unit showed a trend to a slow modification of the firing rate during the recording session, a new background value was calculated.

A variation of the firing rate following drug ejection was defined as a response if it exceeded twice the SD of the mean background activity for at least 20 s (four bins) following microiontophoresis. The magnitude of the effect was defined as the maximum percentage change in the mean firing rate with respect to the mean background activity.

In the presence of an antagonist, a response was considered blocked when its magnitude was reduced by more than 70%, and partially blocked when it was reduced by 50–70%. To verify whether two sets of results belonged to the same population Student's *t*-test (or the Mann-Whitney *U*-test for normalized data) was used. The software allowed the fitting of data to various models, but a linear fit was chosen whenever no non-linear fit was found to be significantly better ($P<0.05$) than the linear one. Curve fittings were compared using an *F*-test.

The last recording site of each penetration was marked by iontophoretic application of Pontamine Sky Blue (cathodal current 10–20 μA, 10–15 min).

At the end of the experiment the rat was killed by an overdose of anesthetic, and the brain removed and kept for 3 days in 10% formalin. The electrode tracks and the recording sites were identified in serial brainstem coronal sections (50 μm thick) stained with Neutral Red.

Results

Ninety-two of the units studied were histologically identified as in the RN, and 36 were antidromically activated by stimulation of the RST. The mean background firing rate of these units was 20.7±5.2 spikes s^{-1} (standard error), values ranging from 10 to 26 spikes s^{-1}.

The firing rate of almost all neurons studied (97%) was influenced by 5-HT. The mean firing rate of the majority of the units (89%) was enhanced – an effect which lasted for up to 6 min after the end of 5-HT ejection. The firing rate then decreased, returning to the background value (Fig. 1A).

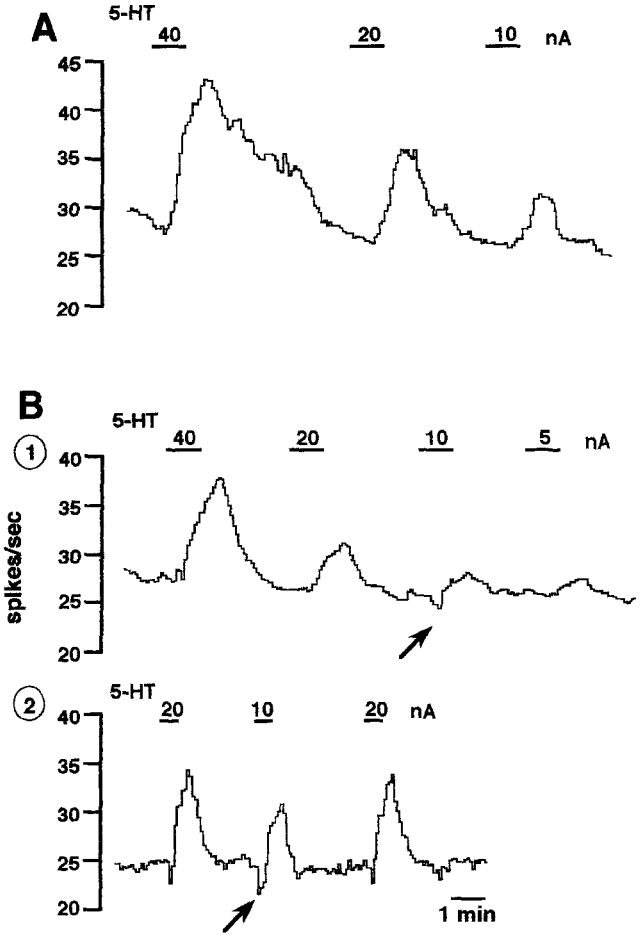

Fig. 1A, B Rate histograms (5 s bins) of neuronal activity of three red nucleus (RN) neurons during microiontophoretic ejection of 5-hydroxytryptamine (5-HT). The *horizontal bars* above the histograms indicate the duration of the ejection periods (30 or 60 s) at the currents given. **A** Pure excitatory responses to 5-HT ejection. **B** (1) A short-lasting inhibitory phase precedes the excitatory response to 5-HT at an ejection current of 10 nA (*arrow*). In the same unit 5-HT ejection at intensities higher (20–40 nA) or lower (5 nA) than 10 nA evoke pure excitatory responses. (2) Excitatory response to 5-HT preceded by a short-lasting (5 s) inhibitory phase that is prolonged up to 20 s by an ejection current of 10 nA (*arrow*)

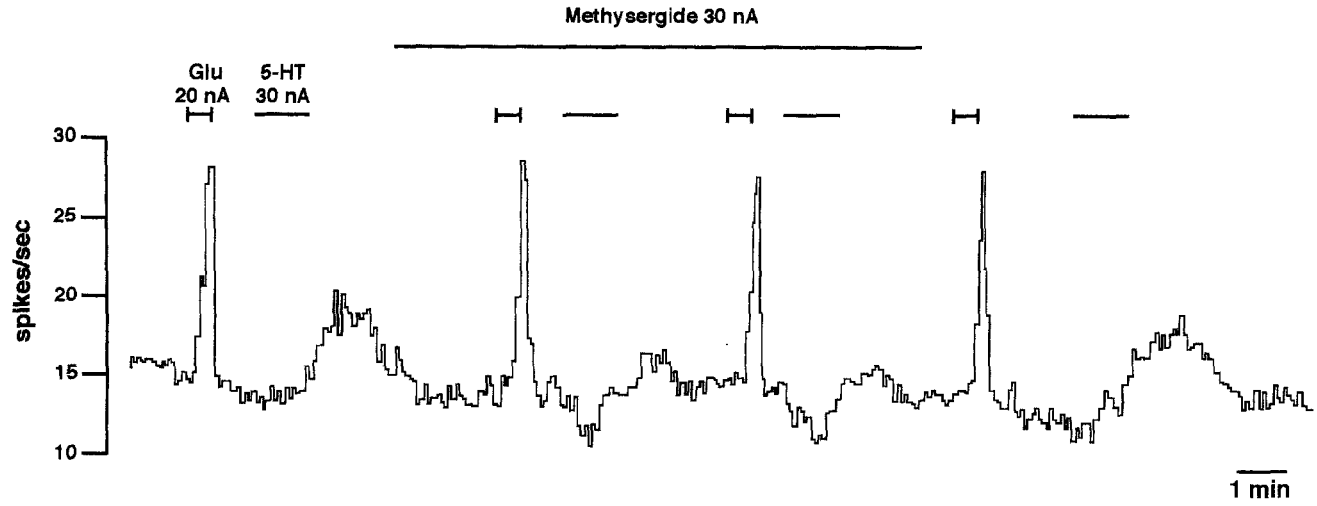

Fig. 2 Rate histogram (5 s bins) of neuronal activity of an RN neuron showing the effect of methysergide on the 5-HT-evoked response. The excitatory response to 5-HT was reversed to an inhibitory effect during methysergide ejection, whereas the response to the excitatory transmitter glutamate (*Glu*), used as a control, was unaffected

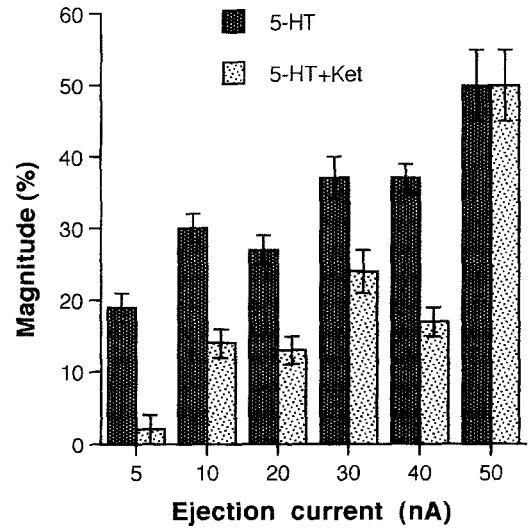

Fig. 3 5-HT dose-response mean values calculated in 6 RN neurons before and during a fixed application (15 nA) of the 5-HT_2 receptor antagonist ketanserin (*Ket*)

Although 5-HT excited the majority of cells, the long-lasting firing enhancement of 19 cells was preceded by a short-lasting inhibition. There was no significant difference between the mean background firing rate of neurons exhibiting pure excitatory responses (22.6±7.7 spikes s^{-1}, n=63) and those in which excitation was preceded by inhibition (19.2±6.2 spikes s^{-1}, n=19).

The inhibitory effects were generally evoked at particular intensities of ejection current and, in many cases, the magnitude of the decrease in the firing rate never exceeded 2 spikes s^{-1} (Fig. 1B). As the reduction of the firing rate was followed by a strong enhancement of firing in the majority of cases, these responses could be classified as biphasic but unbalanced effects, excitations being stronger and longer-lasting than inhibitions. Uniphasic inhibitions of firing were recorded in 7 units.

Excitatory responses to 5-HT were recorded in 75% of the RN neurons which projected to the spinal cord (27 of 36) and in 64% of those which did not (36 of 56). These differences were not significant (two-by-two contingency table, Fisher's test).

A significant dose-response correlation was found in each of the responsive cells with regard to the excitatory effects. In fact, magnitudes progressively and significantly increased up to an ejection current of 50 nA. Higher currents generally induced irreversible modifications in shape and amplitude of the action potentials.

Methysergide (30 nA) blocked excitatory responses to 5-HT totally in 3 of the 5 neurons tested and partially in the other 2. Furthermore, in 2 cases, 5-HT-evoked responses reversed from excitatory to inhibitory during administration of methysergide. This 5-HT antagonist did not depress either background firing rate or glutamate-evoked excitations (Fig. 2).

The 5-HT_2 antagonist ketanserin, tested on 7 neurons, was partially effective in antagonizing 5-HT-evoked responses. Mean magnitudes of the responses to 5-HT before and during 15 nA ketanserin ejection, calculated in 6 neurons, indicated (Fig. 3) that this drug significantly antagonized (P<0.05) the effects of 5-HT produced by ejection current intensities up to 40 nA , but was ineffective when 5-HT was ejected with currents of 50 nA. Under such conditions, by increasing the ketanserin ejection current, 5-HT-evoked responses could be blocked but the background firing rate was depressed. The partial block of the excitatory responses lasted 5–20 min after the end of ketanserin ejection. In 2 cases, the inhibitory component of the response to 5-HT appeared enhanced by ketanserin administration, and this effect persisted for as long as the partial block of the excitatory responses.

The 5-HT_{1A}/5-HT_2 antagonist spiperone was tested in 6 neurons, the firing of 4 of which was transiently inhibited by 5-HT before excitation. Small currents were used to eject this drug because, by increasing the ejection current, spiperone produced responses consistent with enhancements of the effects of the agonist such that both

Fig. 4 Rate histogram (5 s bins) of neuronal activity showing the response to ejection of the 5-HT_{1A} receptor agonist 8-OH-DPAT and the effect of the 5-HT_2 receptor antagonist ketanserin on a biphasic response to 5-HT

components of the 5-HT responses were enhanced. Small ejection currents (5–10 nA) of spiperone, applied for 5–10 min, antagonized the excitatory responses to 5-HT and also the transient inhibitory effects in 3 of 4 neurons. The ejection currents of spiperone required to block the inhibitory components of the responses to 5-HT were 2–3 nA higher than those used to block the excitatory responses. A 5-HT-evoked excitatory response was partially reversed into an inhibitory one during administration of spiperone at an ejection current of 10 nA. Further increasing ejection current intensity converted the response into a strong excitatory effect.

To ascertain a possible contribution of 5-HT_{1A} receptors to the 5-HT-evoked responses, the 5-HT_{1A} agonist 8-OH-DPAT was tested in 10 neurons. In 6 of them it induced a modest, albeit significant, inhibitory response. This effect lasted up to the end of the ejection, and had a mean magnitude of 15±30% at a current of 20 nA. In 2 cases the inhibitory response to 8-OH-DPAT was followed by a late excitation (Fig. 4). In all neurons responsive to 8-OH-DPAT, 5-HT evoked an excitatory response; in 5 cases this was preceded by a short-lasting inhibition, at least for some current intensities. One of these inhibitory effects was antagonized by spiperone whereas two of them were enhanced by ketanserin. An example of this behavior is shown in Fig. 4. Three of the 4 neurons unresponsive to 8-OH-DPAT were excited by 5-HT application. In the remaining neuron 5-HT evoked a short-lasting inhibition that was enhanced by spiperone.

Discussion

These results demonstrate that in the RN both rubrospinal and non-rubrospinal neurons are strongly responsive to 5-HT to the same extent. In fact, a typical generalized response to 5-HT – a long-lasting, dose-dependent increase of the mean firing rate – was recorded from neurons scattered throughout the nucleus.

The RN neuronal responses to 5-HT raise two questions inherent to the specificity of these effects and their functional significance. A high probability exists that firing enhancements induced by 5-HT are mediated by 5-HT receptors. In fact these responses were blocked by methysergide, a non-selective antagonist of 5-HT receptors (Zifa and Fillion 1992), and by ketanserin, a 5-HT_2 antagonist (Leysen et al. 1987). It can be excluded that 5-HT antagonists depress excitability of RN neurons as they blocked 5-HT-evoked firing enhancements selectively, without affecting excitation by glutamate. In addition, these results were consistent with those induced by spiperone, a 5-HT_2/5-HT_{1A} antagonist (Pedigo et al. 1981). Therefore, excitatory responses to 5-HT application could be mediated by 5-HT_2 receptors; such receptors have been previously reported in the nucleus (Pazos et al. 1985).

Even if the excitatory responses to 5-HT appear mostly due to 5-HT_2 receptors, it is noteworthy that, at high intensities of ejection current, the magnitudes of 5-HT-evoked effects were scarcely influenced by ketanserin. Therefore we cannot exclude the possibility that massive doses of 5-HT are able to recruit receptors other than 5-HT_2. These results suggest also that at least some of the short-lasting inhibitory effects induced by 5-HT in RN neurons are specific. In fact, 8-OH-DPAT, a known selective agonist of 5-HT_{1A} receptors, induced weak inhibitory responses in the same RN neurons which exhibited a transient inhibitory component in their response to 5-HT application. Furthermore, spiperone blocked inhibitory components of 5-HT-evoked responses. The hypothesis of a participation of 5-HT_{1A} receptors in the 5-HT-evoked responses is in agreement with immunohistochemical data giving evidence of the presence of 5-HT_1 receptors in the RN (Pazos and Palacios 1985). In this context, the late excitation induced by 8-OH-DPAT in 2 neurons might arise from inhibition by the same 8-OH-DPAT of GABAergic interneurons. These 5-HT_{1A} receptors probably coexist in RN with 5-HT_2 receptors, as some inhibitory components in the response to 5-HT were unmasked only in the presence of ketanserin which antagonized the excitatory components.

It could be that at least some of the short-lasting inhibitory responses were due to an interaction of 5-HT with the mechanisms regulating GABA release by interneurons. In fact, the close proximity of some serotoninergic terminals to GABAergic terminals provides some plausibility to this hypothesis (André et al. 1987). In addition, the poor dose-response correlation of the inhibitory components in the responses to 5-HT administration suggests an interference of 5-HT with other neurotransmitters, a hypothesis already tested and verified in other

central structures (Mayer and Straughan 1981; Lee et al. 1986; Akasu 1988; Hicks et al. 1989; Strahlendorf et al. 1989). Finally, we cannot exclude the possibility that excitation by 5-HT of GABAergic interneurons may contribute to inhibition, although an increase in "noise" during the inhibition was never observed.

The functional significance of the 5-HT influence on RN neurons is an open question. The serotoninergic control does not appear limited to a selected group of RN neurons, defined either functionally or anatomically. In this regard, the physiological evidence furnished by our results is corroborated by morphological data indicating that serotoninergic fibers are scattered throughout the whole RN (Bosler et al. 1983; Steinbusch 1984). Also the subset (23%) of responsive units characterized by biphasic responses to 5-HT and specifically by the initial short-lasting inhibition appeared neither to be confined to a selected RN area nor to share a common target for their projection. It remains to be verified whether the units exhibiting a homogeneous response to 5-HT administration receive the same type of afferents and therefore process similar information.

The serotoninergic system has traditionally been related to the control of nociceptive function. The responses to nociceptive stimuli recorded in the RN were inhibitory in nature (Matsumoto and Walker 1991). As the effects induced by 5-HT were mostly excitatory, the hypothesis that serotoninergic fibers deliver nociceptive information must be ruled out. It cannot be excluded, however, that the 5-HT-evoked short-lasting inhibitions recorded in a subset of RN neurons are an expression of nociceptive control. In this context, 5-HT could also exert an indirect influence on RN neurons by GABAergic fibers. An interesting test would be to establish how neuronal RN activity is influenced by electrical activation of the serotoninergic path from the dorsal raphe to RN.

The strongest, most general effect of 5-HT application in the nucleus is the enhancement of the neuronal background firing and therefore of the RN output. This nucleus participates in motor control, and mostly in the initiation phase of the movement (Dormont et al. 1989) contributing to the management of conditioned and unconditioned reflex responses (Bracha et al. 1993). Further evidence of the rubral functions is given by the observation that cooling the RN (Amalric et al. 1983) as well as its chemical reversible inactivation (Martin et al. 1993) increases motor reaction and execution times.

The strong influence exerted by 5-HT on RN neuronal firing is in agreement with the observation that, at least in cats, motor performance is influenced by the 5-HT content of the RN (Schmied et al. 1991). Our results are also in line with our previous observations in another subcortical motor structure, the lateral vestibular nucleus (Licata et al. 1990). Specifically, magnitudes and percentages of excitatory responses to 5-HT in the RN were comparable to those observed in the lateral vestibular nucleus. As vestibular and rubral control are exerted mostly on extensor and flexor muscles, respectively, the neuronal responses to 5-HT recorded in these two nuclei suggest a generalized, and almost symmetrical, excitatory action of 5-HT on motor activity.

In fact, a recent hypothesis is that the primary function of the serotoninergic system is that of facilitating motor output, simultaneously inhibiting the processing of sensory information (Jacobs and Fornal 1993). Some caution should, however, be exercised when extending this hypothesis to other motor structures. Although it has been ascertained that 5-HT is excitatory on motoneurons (McCall and Aghajanian 1979; Takahashi and Berger 1990), this is not true in other structures, such as motor or cerebellar cortex, where the effects of 5-HT are controversial and often inhibitory (Jordan et al. 1972; Strahlendorf et al. 1984). Also, a significant percentage of neurons of the superior and medial vestibular nuclei, involved in the very specific motor function of the oculomotor control, exhibited inhibitory or biphasic responses to microiontophoretic 5-HT (Johnston et al. 1993; Licata et al. 1993a,c).

The facilitatory influence of 5-HT on RN background neuronal activity has been demonstrated, but the modalities and functional characteristics of this facilitation remain to be ascertained. An important point to be clarified is to what extent the enhancement of the background firing rate is associated with an increased or depressed responsiveness to cortical and cerebellar inputs.

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