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# Serotonergic modulation of spinal motor control

Jean-François Perrier[1] and Florence Cotel[2]

Serotonin (5-HT) is a monoamine that powerfully modulates spinal motor control by acting on intrasynaptic and extrasynaptic receptors. Here we review the diversity of 5-HT actions on locomotor and motoneuronal activities. Two approaches have been used on *in vitro* spinal cord preparations: either applying 5-HT in the extracellular medium or inducing its synaptic release. They produced strikingly different results suggesting that the net effect of 5-HT depends on the identity of the activated receptors and their location. Recent findings suggest that moderate release of 5-HT facilitates locomotion and promotes the excitability of motoneurons, while stronger release inhibits rhythmic activity and motoneuron firing. This latter effect is responsible for central fatigue and secures rotation of motor units.

**Addresses**
[1] Department of Neuroscience and Pharmacology, University of Copenhagen, Denmark
[2] Queensland Brain Institute, University of Queensland, Australia

Corresponding author: Perrier, Jean-François (Perrier@sund.ku.dk)

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## Introduction

The role of serotonin (5-hydroxytryptamine, 5-HT) as regulator of motor patterns has been extensively studied during the past fifty years. Several publications have demonstrated that 5-HT has multiple effects on spinal motor circuits. In the present article, we review the literature demonstrating that exogenous application of 5-HT induces multiple and contradictory effects on spinal rhythmic activities and on motoneuron excitability. We argue that the heterogeneity of these actions only makes sense when considered under more physiological conditions: that is, when 5-HT is released from synapses and differentially activates receptors depending on their locations and affinities.

## Organization of the serotonergic system

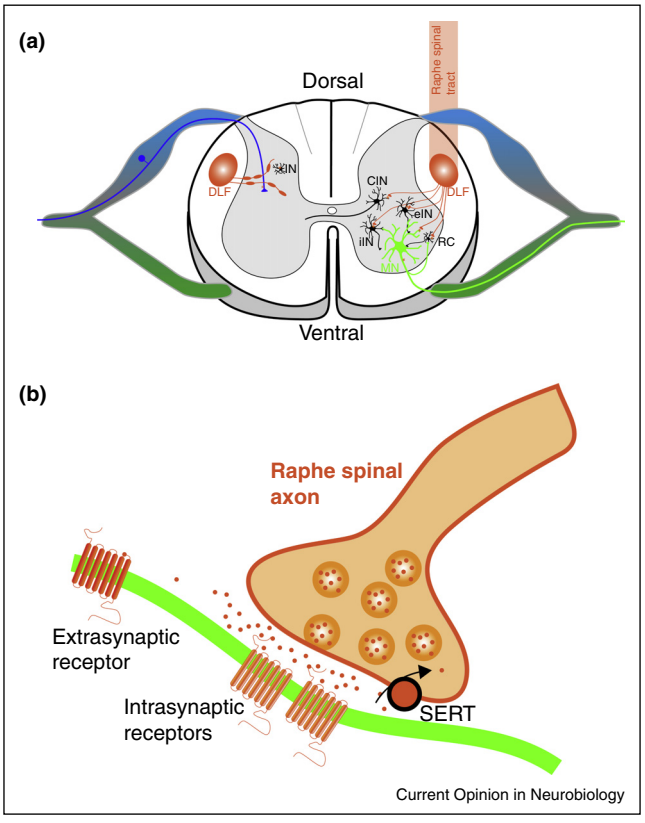
5-HT is a neurotransmitter that is mainly synthetized in neurons in the brainstem raphe nuclei. The raphe spinal pathways originate from *raphe obscursus*, *raphe pallidus*, *raphe magnus* and *raphe dorsalis* to terminate at all levels along the spinal cord [1,2]. In the dorsal horns, where sensory information is processed, serotonergic varicosities are characterized by non-synaptic contacts suggesting a paracrine mode of release [3]. By contrast, in the ventral horn, raphe spinal neurons make well-defined synaptic contacts on interneurons and motoneurons [4,5] (Figure 1). Once released, 5-HT binds to receptors in the 15-member serotonin receptor family. With the exception of 5-$HT_3$, 5-HT receptors are coupled to G proteins of the Gi/o, Gs and Gq subgroups [6]. This indicates that 5-HT can trigger a wide variety of regulatory actions. Indeed, in spinal cord neurons, 5-HT was shown to facilitate $Na^+$, $Ca^{2+}$, cations currents, to inhibit $K^+$, $Ca^{2+}$, $Na^+$ currents and to modulate synaptic transmission (see Perrier *et al.* [7•] for review). 5-HT receptors have different affinities for their natural ligand, the 5-$HT_1$ and 5-$HT_7$ receptors presenting the highest binding affinity (see Table 1 in Murray *et al.* [8] for an exhaustive review). Most serotonergic receptors are present in the spinal cord. They are expressed presynaptically and in the somato-dendritic compartments [7•,9–15]. Some of the receptors such as the 5-$HT_{1A}$ and 5-$HT_{2A}$ have been detected outside serotonergic synaptic innervation [16••,17], suggesting that they are activated by a background concentration of 5-HT present in the extracellular space and/or by spillover occurring during intense synaptic activity of the raphe spinal pathway. 5-HT is cleared from the extracellular space by a specific transporter (SERT) located in the terminals and varicosities of raphe spinal neurons (Figure 1b). The expression of SERT parallels the serotonergic innervation [18] suggesting that 5-HT is removed at different rates in distinct extracellular compartments of the spinal cord.

The heterogeneity of 5-HT receptors in terms of affinity, subcellular location and intracellular activated pathways makes it virtually impossible to predict how synaptic release of 5-HT may affect motor control. Interestingly, neurons in the raphe nuclei fire regularly at frequencies tightly correlated with motor activities [19]. This suggests that the amount of 5-HT released in the spinal cord varies in parallel with movement intensity. This important point indicates that 5-HT receptors are not activated together under physiological conditions. Instead the moderately active raphe spinal pathway may preferentially activate sub-synaptic and high affinity receptors while high levels of activity may also increasingly recruit low affinity and extrasynaptic receptors.

## Serotonin differentially regulates rhythmic activity in the spinal cord

Locomotion, such as walking or swimming, is orchestrated by a subset of interneurons located in the ventro-medial

**Figure 1**




Organization of the raphe spinal pathway. **(a)** The raphe spinal tract located in the *dorsolateral funiculus* (DLF) releases 5-HT in a paracrine manner in the dorsal horn and makes well defined synaptic contacts on different neurons from the ventral horn. CIN: commissural interneuron; eIN: excitatory interneuron; iIN: inhibitory interneuron; RC: Renshaw cell; MN: motoneuron. **(b)** Once synaptically released 5-HT binds to intrasynaptic and extrasynaptic receptors before being recaptured by a specific transporter (SERT).

part of the spinal cord [20]. Most interneurons from this area, receive dense serotonergic synaptic innervation including the Renshaw cells that mediate recurrent inhibition of motoneurons [21,22] (Figure 1). These observations suggest that 5-HT modulates locomotor activity. In agreement, several studies demonstrated that bath application of 5-HT in *in vitro* spinal cord preparations triggers fictive locomotion characterized by rhythmic activities in muscles or in limb motor nerves [23,24]. However, the effects induced by 5-HT on locomotion are not straight forward and the heterogeneity of the observations reported reflects the complexity of the modulation. Fictive locomotion is usually characterized by parameters such as cycle period, amplitude of bursts of activity recorded in individual motor nerves, coordination between left and right or between ventral roots preferentially innervating flexor and extensor muscles.

Few studies reported that an exogenous application of 5-HT on the spinal cord increases locomotion speed. In zebrafish larvae, 5-HT decreases the interburst interval [25]. Similar findings were reported in the newborn rat where 5-HT significantly decreases the period of the locomotor cycle in a dose-dependent manner [23]. By contrast, most other studies performed in the lamprey, frog embryo, juvenile zebrafish, neonatal rat and mouse reported an inhibitory effect of 5-HT characterized by a dose-dependent increase of the cycle period [26–32]. There is a general agreement that this inhibitory effect is caused by the activation of 5-$HT_1$ receptors [26–28,33]. Exogenous application of 5-HT also increases the coordination between limbs and between flexor and extensor muscles [13,31,34–36]. These effects are mediated by 5-$HT_2$ and 5-$HT_7$ receptors [13,31,35]. The activation of serotonergic receptors in commissural interneurons increases their excitability by promoting L-type $Ca^{2+}$ channels and by inhibiting N and P/Q type $Ca^{2+}$ channels. This latter effect prevents the activation of $Ca^{2+}$-dependent $K^+$ channels, thus increasing the firing of commissural interneurons and thereby the left-right coordination [37,38]. At high speed, left-right coordination is secured by the recruitment of V2a interneurons [39]. 5-HT promotes the excitability of these excitatory interneurons that project to ipsilateral commissural interneurons [40–42]. Since the release of 5-HT increases with locomotion speed [19], we postulate that it contributes to the progressive recruitment of V2a interneurons thereby preventing a switch from trotting to galloping at high speeds.

The heterogeneity of the effects induced by exogenous application of 5-HT can be explained by the multiplicity of receptor subtypes that get activated simultaneously. In comparison, under physiological conditions, endogenous 5-HT differentially binds receptors with a preference for intrasynaptic and high-affinity subtypes. We believe synaptic release of 5-HT is necessary for understanding how 5-HT modulates locomotion. Only few studies have used such an approach. Recently, the group of Whelan evoked locomotion in a brainstem-spinal cord preparation by electrical stimulation of the brainstem and investigated the role of endogenous 5-HT by increasing its release with the Selective Serotonin Reuptake Inhibitor (SSRI) citalopram [27]. Compared to exogenous 5-HT, citalopram increases the concentration of the neuromodulator inside and near synapses. Not surprisingly, they found that the effects induced by the SSRI differed from those induced by exogenous application of 5-HT. Both approaches induce an increase in the duration of the locomotor cycle. However, contrary to exogenous 5-HT, citalopram decreases the coordination measured between left/right sides and between flexors and extensors. Pharmacological analysis suggests that the increase in cycle duration is mediated by 5-$HT_1$ receptors. By contrast, the activation of 5-$HT_2$ and 5-$HT_7$ receptors has an excitatory effect. Based on their findings, the authors