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Original
Histamine modulates spinal motoneurons and locomotor circuits / Coslovich, T., Brumley, M.R., D'Angelo, G., Della Mora, A., Swann, H.E., Ortolani, F., Taccola, G.. - In: JOURNAL OF NEUROSCIENCE RESEARCH. - ISSN 0360-4012. - 96:5(2018), pp. 889-900. [10.1002/jnr.24195]

Availability:
This version is available at: 20.500.11767/62139 since: 2017-11-15T09:47:00Z

Publisher:

Published
DOI:10.1002/jnr.24195

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07 November 2026

Histamine modulates spinal motoneurons and locomotor circuits

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Running title: histamine modulates lumbar motor activity

Associate editor: Bertrand Lambolez

Support or grant information: HES was supported by NIGMS P20GM103408. GT is supported by funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie (grant agreement No 661452).

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histamine modulates lumbar motor activity

Abstract

Spinal motoneurons and locomotor networks are regulated by monoamines, among which the contribution of histamine has yet to be fully addressed. The present study investigates histaminergic regulation of spinal activity, combining intra- and extracellular electrophysiological recordings from neonatal rat spinal cord in vitro preparations. Histamine dose-dependently and reversibly generated motoneuron depolarization and action potential firing. Histamine (20µM) halved the area of dorsal root reflexes and always depolarized motoneurons. A transitory repolarization was shown by the majority of cells, while 37% showed a sustained depolarization maintained with intense firing. Extracellularly, histamine depolarized ventral roots (VRs), regardless of blockage of ionotropic glutamate receptors. Initial, transient glutamate-mediated bursting was synchronous among VRs with some bouts of locomotor activity in a subgroup of preparations. After washout, amplitude of spontaneous tonic discharges increased. No desensitization or tachyphylaxis appeared after long perfusion or serial applications of histamine. On the other hand, histamine, induced single motoneuron and VR depolarization even in the presence of tetrodotoxin (TTX). During chemically-induced fictive locomotion (FL), histamine depolarized VRs. Histamine dose-dependently increased rhythm periodicity and reduced cycle amplitude until near suppression. This study demonstrates that histamine induces direct motoneuron membrane depolarization and modulation of locomotor output, indicating new potential targets for locomotor neurorehabilitation.

histamine modulates lumbar motor activity

Significance Statement: Neurons and neural circuits in the spinal cord are regulated by monoamines, among which the contribution of histamine has yet to be fully addressed. The present study investigated histaminergic regulation of spinal activity, combining intra- and extracellular electrophysiological recordings from the isolated spinal cord of the neonatal rat. Findings suggest that histamine modulates spinal motor systems, including locomotor networks. This is important for understanding how histamine may influence motor systems and spinal cord plasticity following spinal cord trauma.

Keywords: Central Pattern Generator, motoneuron, sustained depolarization, fictive locomotion

Abbreviations: CCF, cross-correlation function; DR, dorsal root; DRG, dorsal root ganglion; DVRPs, dorsal root ventral root potentials; FFT, fast fourier transform; FL, fictive locomotion; NMDA, N-Methyl-D-aspartic acid ; P, postnatal; Th, threshold; TTX, tetrodotoxin; VR, ventral root; 5-HT, 5-hydroxytryptamine.

Histamine modulates spinal motoneurons and locomotor circuits

Introduction

Physiological activities integrated in the spinal cord are finely tuned by descending modulatory systems that are essential to obtain proper adjustment of desired locomotor outputs (Harris-Warrick, 2011). For instance, neuromodulators are involved in the generation, timing, amplitude, and development of spinal locomotor networks through complex interactions among neuromodulatory inputs (Miles & Sillar, 2011). The monoamines are known to play an important role in regulating spinal locomotor activity (e.g., Cazalets et al. 1992; Kiehn & Kjaerulff, 1996; Sqalli-Houssaini & Cazalets, 2000; Madriaga et al., 2004; Beliez et al., 2014). However, within this family of molecules, the specific role of histamine remains unknown. Several studies, including those based on central pattern generator models, indicate a role for this biogenic amine in tuning rhythmic bursting in invertebrates (Pearlstein et al., 1998; Matsuura et al., 2002; Le et al., 2006; Sullivan et al., 2007; Buhl et al., 2008).

In the spinal cord, histamine is released by descending fibers departing from the tuberomamillary nucleus of the posterior hypothalamus, where central histaminergic neurons are localized exclusively (for review see Haas et al., 2008). Histamine is also present in peripheral neurons such as dorsal root ganglia (DRG), sending projections to the spinal cord (Häppölä et al., 1991; Nissinen et al., 1995). Notably, histamine-immunoreactive fibers have been described as located around the central canal (Inagaki et al., 1988) and scattered in the anterior horn of the lumbar cord with a reported maximum density in lamina X (Seybold, 1985). In this area, a class of interneurons (Al-Mosawie et al., 2007; Bertrand & Cazalets, 2011) has been related to the activity of spinal circuits involved in the generation of locomotor patterning (Grillner, 2006). Four metabotropic histamine receptors have been described in the CNS ($H_{1\text{-}4}$; Haas et al., 2008), and are also found in spinal tissue (Taylor et al., 1982 for H_1 subtype; Murakami et al., 1999 for H_2;

Cannon et al., 2007 for H_3; Strakhova et al., 2009 for H_4). The effects of H_1 and H_2 receptor activation on spinal motoneurons has been described (Constanti & Nistri, 1976; Taylor et al., 1982; Saito et al., 1984; Wu et al., 2012).

Although the spinal locomotor rhythm seems to emerge from an essentially glutamatergic core (Grillner & Jessel, 2009), and GABA and glycinergic inhibitory connections are responsible for formation of the alternating pattern among flexor-extensor motor pools on the two sides of the cord (Beato & Nistri, 1999), a wide list of neuromodulators contributes to refining the timing and features of the network to optimize motor output (Harris-Warrick, 2011; Miles & Sillar, 2011). Currently, it is still to be clarified how histamine participates in the regulation of such spinal rhythmic activity in mammals. Therefore in the present study, we explored the role of histamine in modulating motoneuron membrane properties and synaptic activity in rhythmogenic ventral interneuronal networks in the spinal cord. To achieve this aim, we used intra- and extra-cellular electrophysiological techniques. Given the crucial role of monoamines in regulating spinal function, we hypothesized that ventral motor network output would be modulated by application of histamine. These issues were investigated using an in vitro neonatal rat spinal cord, a model useful for examining spinal and locomotor function at circuit and cellular levels (Brumley et al, 2017).

Methods

Whole spinal cord preparations and extracellular recordings

All procedures were approved by the International School for Advanced Studies (SISSA) ethics committee and are in accordance with the guidelines of the National Institutes of Health (NIH) and with the Italian Animal Welfare Act 24/3/2014 n. 26 implementing the European Union directive on animal experimentation (2010/63/EU).

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Experiments were performed on isolated spinal cords from Wistar neonatal rats (0 - 4 day old), as previously reported (Taccola et al., 2012). All measures were taken to reduce the number of animals used and to minimize their suffering. Male and female animals were equally and randomly selected for the study.

Spinal cords (sectioned from the midthoracic region to the *cauda equina*) were placed in a small recording chamber (at room temperature) and continuously superfused (5 mL/min) with Krebs solution of the following composition (in mM): 113 NaCl, 4.5 KCl, 1 $MgCl_2 7H_2O$, 2 $CaCl_2$, 1 NaH_2PO_4, 25 $NaHCO_3$, and 11 glucose, gassed with 95 % O_2-5 % CO_2, pH 7.4. Motoneuron pool activity was extracellularly recorded from a lumbar ventral root (VR) using tight-fitting monopolar suction electrodes. Borosilicate glass electrodes (Harvard Apparatus, MA, USA) containing an Ag^+/AgCl pellet and filled with physiological solution were connected to a DC-coupled differential amplifier (DP-304 differential amplifier, Warner Instruments, CT, USA; Taccola et al., 2012).

Recordings from motoneurons

Sharp electrode intracellular recordings (electrode resistance = 43.52 ± 12.54 MΩ) were obtained from a total of 115 lumbar (L) motoneurons, from both left (l) and right (r) L3 - L5 segments of spinal cords isolated from neonatal rats of postnatal (P)0 – P4 days. Cells were antidromically identified by delivering a train of electrical pulses (2 x Th, 0.1 ms, 5Hz) to a VR, through a programmable stimulator set in current output (STG 4002®; Multi Channel Systems, Reutlingen, Germany). Motoneurons were impaled using borosilicate glass microelectrodes (Harvard Apparatus, MA, USA) filled with 3 M-KCl (30–60 MΩ resistance) in current-clamp conditions (Axoclamp® 900A amplifier, Molecular Devices, LLC, CA, USA).

In control conditions, cells showed an overall average resting potential of - 66.00 ± 9.70 mV, with a membrane resistance of 51.86 ± 31.59 MΩ and an antidromic spike amplitude of 60.52 ± 11.28 mV. Input resistance of motoneurons was obtained by delivering steps of current

(amplitude from −0.8 to 0.8 nA, duration = 80 ms; Axoclamp® 900A amplifier, Molecular Devices, LLC, CA, USA). Current/voltage plots were linear within the voltage range recorded, with the slope indicating cell input resistance. To suppress synaptic input onto motoneurons, the broad sodium channel blocker, tetrodotoxin (TTX; Ascent Scientific, Bristol, UK), was applied at the concentration of 1 µM to reach the quick and complete disappearance of electrically evoked antidromic spikes (4-5 min). Afterwards, concentration of TTX was halved (0.5 µM) and continuously provided to maintain a stable sodium current block (Dose et al., 2014). This concentration remains slightly higher than the one (0.3 µM) indicated to abolish spinal reflexes (Otsuka and Yanagisawa, 1980) and able to completely block the conduction of action potentials in the isolated spinal cord (Yanagisawa and Otsuka, 1990). To confirm that the halved TTX concentration does not change membrane potentials, continuous intracellular recordings were taken from seven motoneurons during a long perfusion with TTX 1µM, followed by TTX 0.5 µM, showing no polarization after decreasing TTX concentration (mean polarization = 0.12 ± 1.04 mV, Wilcoxon Signed Rank Test, W= 8.000, Z-Statistic = 0.676, P = 0.578, n = 7).

Parameters of spinal network activity

Spontaneous ventral root (VR) activity was quantified by power spectrum analysis adopting Fast Fourier Transform (FFT) in Clampfit® 10.3 software (Molecular Devices Corporation, PA, USA). Dorsal root (DR) electrical rectangular stimuli (0.1 ms, 0.33 Hz; STG 4002®; Multi Channel Systems, Reutlingen, Germany) were used to evoke single VR responses that were recorded from the ipsilateral VR of the same segment. Stimuli were considered either low or high threshold (Th), upon their ability to elicit fast synaptic responses from the corresponding VR (see Taccola et al., 2012).

Rhythmic fictive locomotion (FL) was recorded as routine, from L1-2 VRs which mainly express flexor motor commands to hindlimb muscles, and from L5 VRs which mainly convey

extensor motor signals to the same limbs (Kiehn & Kjaerulff, 1996; Gabbay et al., 2002). The alternation of discharges displayed between flexor and extensor motor pools and between the left (l) and right (r) sides of the cord represents the trademark of FL (Kiehn, 2006). FL was elicited by continuous bath-application of N-methyl-D-aspartatic acid (NMDA 5 µM) plus serotonin (5-hydroxytryptamine; 5-HT; 10 µM; Cazalets et al., 1992). A cycle was defined as a period of sustained membrane depolarization originating with onset from baseline, remaining above a preset threshold (usually 5 times the standard deviation of baseline noise) for > 400 ms (Bracci et al., 1996). FL cycles (at least 20) were analyzed for their periodicity (time between the onset of two cycles of oscillatory activity), amplitude and regularity, expressed by the coefficient of period variation (CV). Cross-correlation function (CCF) was performed using Clampfit® 10.3 software (Molecular Devices Corporation, PA, USA), in order to determine the correlation among signals arising from pairs of VRs. While a CCF > + 0.5 indicates that two roots are synchronous, CCF < - 0.5 shows full alternation.

Statistical analysis

Data are expressed as mean and SD, while *n* indicates the number of spinal cord preparations analyzed. Statistics were performed using SigmaStat® 3.5 software (Systat Software, CA, USA). Using a normality test, all parametric values were analyzed with Student's t-test (paired or unpaired) in order to compare two groups of data, or with ANOVA for more than two groups. For non-parametric data, a Mann-Whitney test was performed for two groups and with Friedman repeated measures ANOVA on ranks for multiple comparisons. Multiple comparisons, ANOVA was applied first and then followed by a post hoc Tukey test for groups > 2. Results were considered significant when $P < 0.05$.

Drugs

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Pharmacological identification of histamine-mediated effects has been conducted within the range of histamine concentrations measured in the spinal cord (Kuruvilla et al., 1985). Effects of a long-term application of histamine were assessed by incubating the spinal cords in a histamine solution (20 µM) overnight. On the following day, spinal cords were moved to the recording chambers continuously superfused with histamine. Once suction electrodes were mounted and baseline recordings taken, the drug was washed out using physiological solution. Histamine dihydrochloride (Murakoshi et a., 1985) was purchased from Tocris (Bristol, UK). N-Methyl-D-aspartic acid (NMDA) was purchased from Ascent Scientific (Bristol, UK) as well as tetrodotoxin (TTX). Serotonin hydrochloride (5-HT) was purchased from Sigma-aldrich (Milan, Italy).

Results

Locomotor spinal circuits are modulated by biogenic amines (Cazalets et al., 1992; Beliez et al, 2014). Among these, however, the role of histamine has been little explored. Here we investigated whether histamine receptors are functionally present on motoneuron membranes and whether their selective activation plays a role in spinal physiology. In our experiments, intra- and extracellular recordings identified a new role for histamine in modulating spinal motoneurons and locomotor-related interneurons.

Histamine reversibly depolarizes motoneurons in a dose-dependent manner

To investigate whether histamine affects spinal cord function, intracellular recordings were obtained from antidromically-identified motoneurons as a read-out element of the entire spinal cord circuitry. Under current clamp configuration, the exogenous application of 1 µM histamine depolarized the motoneuron membrane potential (shown in Figure 1A) evoking the appearance of sporadic action potentials. These results were confirmed in a set of eight cells, where on

average 1 µM histamine significantly depolarized motoneurons (paired t-test; t_7 = -3.579, P = 0.009; n = 8). In Figure 1B, the cumulative dose-response curve provides an EC_{50} of 8.14 µM histamine and indicates that the mean depolarization in response to 50 µM histamine was significantly greater than with 1 µM (t-test, t_{12} = -2.596, P = 0.023; n = 6, 8). Figure 1C shows a sustained depolarization with superimposed intense firing upon application of 50 µM histamine, with the sampled cell returning to baseline potential after washout. Similar responses were recorded from an additional five motoneurons, using the maximum concentration (50 µM). On average, washing out from higher doses of histamine (20, 50 µM) required 541.81 ± 121.07 s (n = 15).

To verify the presence of functional histamine receptors on motoneuron membrane, we blocked action potential-mediated transmission by using TTX (0.5-1 µM; Dose et al., 2014) before and during histamine application (20 µM). Before histamine application, TTX suppressed spontaneous tonic activity, abolished action potentials, and hyperpolarized motoneurons (Figure 1D, mean hyperpolarization -3.15 ± 1.82 mV, n = 14). The addition of histamine in the presence of TTX induced a significant depolarization (Figure 1D, E, mean depolarization 2.91 ± 1.15 mV, paired t-test, t_4 = -5.648, P = 0.005, n = 5) without any changes in motoneuron input resistance (31.28 ± 16.69 MΩ in TTX only, 34.12 ± 18.06 MΩ in TTX + histamine 20 µM; paired t-test, t_2 = -0.828, P = 0.495, n = 3).

To further confirm the observations reported from single motoneurons, extracellular recordings from VRs of additional spinal cords showed that histamine depolarized VRs in the presence of TTX (316 ± 108 µV; n = 8).

A single application of histamine elicits two different types of responses from motoneurons

As depicted in the example in Figure 2A, a single application of histamine (20 µM) initially induced a first depolarization peak followed, in the continuous presence of histamine, by a

repolarization with sporadic firing activity. A similar response to histamine was recorded in 20 cells, where the first depolarization appeared after 165.23 ± 98.43 s of perfusion, reaching a steady state depolarization at 10 min application (6.00 ± 2.81 mV).

However, in 37% (12 of 32) of motoneurons tested, a single application of histamine (20 µM) induced a sustained motoneuron depolarization with intense firing, similarly to several aminergic systems (Hounsgaard et al., 1984; Hounsgaard & Kiehn, 1985; Perrier & Cotel, 2008; Bouhadfane et al., 2013).

The sample trace in Figure 2B displays a motoneuron at resting conditions that was manually depolarized until reaching a sustained depolarization with superimposed action potentials. After returning to resting potential, the application of 20 µM histamine induced a sustained depolarization with a superimposed high frequency firing (mean frequency > 3 Hz) transiently abolished by repolarizing the cell to its resting value. On average, the sustained depolarization started after 178.63 ± 77.26 s of perfusion, reaching a sustained depolarization amplitude of 10.05 ± 3.78 mV with superimposed firing at 3.12 ± 2.35 Hz (n = 12).

However, after histamine application, the majority of cells (n = 20) showed only a transient depolarization without any intense firing. This was the case regardless of their resting potential, which was similar among cells that did or did not show sustained depolarization with intense firing (Mann-Whitney rank sum test, T = 266.000, P = 0.968, n = 31, 12). Moreover, in the continuous presence of histamine 20 µM, one cell that lacked both sustained depolarization and repetitive spikes could not recover them, even if depolarized by 12 mV to reach the membrane potential experienced by cells showing sustained depolarization (data not shown). Lower concentrations of histamine (10 µM), never elicited sustained depolarization with high frequency spikes (n = 5).

In summary, a single application of 20 µM histamine always significantly depolarized motoneurons, while also induced a sustained depolarization with high frequency firing in a subset

of the preparations. This dose was therefore used as an operative concentration during extracellular recordings to test the role of histamine in motor pools.

Histamine reduces reflex responses

To investigate if histamine plays a role in modulating synaptic transmission in spinal motor pools, as previously reported in other models (Kissel and Domino, 1959), we tested the effect of histamine on sensory inputs elicited by electrical stimulation of dorsal afferents. We electrically stimulated a DR with trains of rectangular pulses (0.33 Hz) and recorded the evoked reflexes either from VRs (dorsal root ventral root potentials, DRVRPs) or from single motoneurons, both in control and after application of histamine.

Amplitude of DRVRPs evoked by electrical pulses (2 x Th) in the presence of histamine was not significantly different from responses evoked before histamine (90.88 ± 20.59 %; Wilcoxon signed rank test; W = -74.000, Z = -1.913, P = 0.058; n = 16), regardless of the concentration of histamine applied (5-200 µM; 97.96 ± 5.31%; Friedman Repeated Measures Analysis of Variance on Ranks, χ^2 (4) = 2.200, P = 0.699, n = 4). Likewise, in the presence of 20 µM histamine, amplitude of DRVRPs was not affected even by increasing intensities of electrical stimulation (from 1x Th to 8x Th; Kruskal-Wallis one-way ANOVA on ranks, H (7) = 1.116, P = 0.993; n = 5, 9).

Next, we calculated the area of DR reflexes by intracellularly recording from a single motoneuron in control conditions (Figure 3A), or during histamine application after repolarizing cells to their baseline value of resting potential (Figure 3B). With respect to control, the motoneuron in Figure 3B shows reduced spike number and reduced area of DR reflexes in response to histamine (20 µM). The same observation was confirmed in seven cells, in which DR reflex area was significantly halved by histamine (49.12 ± 24.16 % of control; Figure 3C; paired t-

test; $t_6 = 2.627$, $P = 0.039$), as was the mean spike number (52.09 ± 21.99 % of control; paired t-test, $t_6 = 2.473$, $P = 0.048$).

Histamine induces rhythmic activity and depolarizes VRs

As shown above, histamine affects distinct motoneurons differently. As a consequence, the net effect of histamine on the overall motor output of VRs requires further analysis. Figure 4A shows the complex rhythmic pattern emerging from motor pools during long applications (> 50 min) of histamine. Before histamine application, a spontaneous synchronous activity was recorded from four VRs in almost all preparations tested (27 out of 28; Figure 4B, first panel). Histamine application depolarized VRs until reaching a steady state value (on average 435 ± 145 µV; n = 28 preparations). However, VR depolarization waned (after about 20 min) in the continuous presence of histamine and the DC-level completely recovered to initial baseline after 45 min of washout.

At first, histamine evoked transient regular bursting, superimposed on spontaneous tonic activity (Figure 2B, second panel), which later disappeared leaving only a tonic activity (Figure 4B, third panel). Finally, tonic activity spontaneously increased in amplitude after extensive washout (Figure 4B, fourth panel). In the same preparation, rhythmic activity of VRlL2 was quantified by power spectra during control, early and late applications of histamine, and extensive washout (Figure 4C). In a random sample of six preparations, on average, a baseline characterized by a fast tonic activity (0.010 ± 0.006 Hz) was replaced by a slow pace bursting during early histamine application (0.005 ± 0.003 Hz), which eventually disappeared in the continuous presence of histamine, leaving only a fast tonic activity (0.010 ± 0.008 Hz) similar to the late washout phase (0.010 ± 0.008 Hz).

By blocking fast glutamate transmission with CNQX (10 µM) and APV (50 µM), histamine-induced discharges were abolished. VR depolarization was not significantly different from the one elicited by histamine in the absence of CNQX and APV (294 ± 84 µV; P = 0.07; n = 4).

Impressively, in 12 out of 28 (43%) preparations, an epoch of 7 ± 3 intraburst locomotor-like discharges arose from VRs in the early phase of histamine application. Each epoch of oscillations was mutually alternated (mean $CCF_{homosegmental}$ = - 0.78 ± 0.16; mean $CCF_{homolateral}$ = - 0.81 ± 0.14) and had a mean period equal to 3.12 ± 0.89 s and a mean period CV = 0.22 ± 0.08 (note exemplar traces reported in Figure $4A_1$).

The experiment reported in fig. 4D illustrates how the VR rhythm persisted even after long application of histamine (20 µM for 18 hours). Nevertheless, the rhythm disappeared and baseline was fully repolarized (431 µV) after 40 minutes from histamine washout. Results were confirmed by spectral analysis, which quantified the return to baseline activity as soon as histamine was removed after the long application (Fig. 4E; left, control = 0.055 Hz; right, washout = 0.037 Hz). These data demonstrate that spontaneous rhythmicity is not irreversibly affected by a long-term exposure to the agent.

Thus histamine both depolarizes motor pools, regardless of fast ionotropic glutamate receptors, and modulates network excitability, occasionally bringing it to threshold to express an episode of locomotor cycles.

Histamine modulates fictive locomotion

Histamine has a modulatory action over spontaneous rhythmicity. Thus, we wondered whether this agent, like other monoamines (Cazalets et al. 1992; Kiehn & Kjaerulff, 1996; Sqalli-Houssaini & Cazalets, 2000; Madriaga et al., 2004; Beliez et al., 2014), also regulates the rhythmic alternating locomotor pattern from the lumbar spinal cord. To this aim, we examined the effect of histamine on fictive locomotion (FL) induced by neurochemicals (Cazalets et al. 1992).

histamine modulates lumbar motor activity

The sample traces in Figure 5A show that addition of histamine (20 µM) to a stable FL pattern (induced by 5µM NMDA + 10 µM 5HT) depolarized VRs by 194 µV (on average 232 ± 93 µV, n = 23). Histamine dose-dependently increased rhythm periodicity and reduced cycle amplitude. In Figures 5B and 5C, 10 µM histamine augmented the FL period to 114% (of control) without affecting cycle amplitude, whereas 20 µM histamine increased FL period to 166% and reducing cycle amplitude to 75% of control (Fig. 5D). Finally, 50 µM histamine almost completely suppressed FL (Fig. 4E; period = 326% and amplitude = 83% of control). Data pooled from many preparations showed that 10 µM and 20 µM significantly reduced FL period (which was 3.91 ± 1.18 s pre-histamine; Fig 5F; one-way ANOVA on raw data followed by all pairwise multiple comparison procedures with Tukey Test, $P < 0.001$; n = 35, 8, 28). Likewise, mean cycle amplitude was slightly reduced by 10 µM histamine (81.78 ± 24.11 % of control; paired t-test, t_6 = 2,361, P = 0.056; n = 7), and statistical significance was reached at 20 µM (72.56 ± 10.86 % of control; Wilcoxon signed rank test on raw data, W= -253,000, Z-Statistic = -4,107, $P < 0.001$; n = 22).

In summary, 20 µM histamine slowed the FL rhythm and decreased cycle amplitude, suggesting an important role in modulating the locomotor-like activity generated by spinal locomotor circuits.

Discussion

Using electrophysiological techniques on the isolated spinal cord of the neonatal rat, we found that histamine modulates motoneuron membrane properties and synaptic activity of rhythmogenic circuits in the ventral spinal cord. Furthermore, results of this study indicate that histamine plays a functional role in regulating spinal rhythmic activity, including locomotor patterns.

All motoneurons recorded in this study were depolarized by micromolar concentrations of histamine, with an EC_{50} comparable to that within other regions of the CNS (Zhang et al., 2013). In the spinal cord, histamine depresses reflexes induced by electrical stimulation of dorsal afferents, as first reported in spinal cats (Kissel & Domino, 1959). Surprisingly, we found that long, continuous application of histamine (>5 hrs) did not generate desensitization in the spinal cord, as opposed to what has been reported in other neuronal networks (Poole et al., 2008). Likewise, repetitive applications of histamine did not induce any tachyphylaxis as reported elsewhere (Ebersberger et al., 1997). In fact, both direct and cumulative applications of histamine induced comparable responses.

Depolarization induced by histamine is likely due, at least partly, to the presence of histaminergic receptors on spinal motoneuron membranes, as suggested by our experiments where synaptic transmission was blocked. This has been previously reported for H_1 and H_2 receptors in the spinal cord (Constanti & Nistri, 1976; Wu et al., 2012). Interestingly, the extent of depolarization in the presence of TTX was lower than in physiological solution, indicating that most of the effect is indirect, probably due to recruitment of different neurotransmitters, such as glutamate (Garduño-Torres et al., 2007), acethylcholine (Bacciottini et al., 2002: Munari et al., 2013), noradrenaline (Bealer, 1993) and serotonin (Threlfell et al., 2008).

Sustained membrane depolarization (Hounsgaard et al., 1984) is a biophysical cellular property related to standing posture in mammals (Eken et al., 1989), and can be unmasked by modulation of calcium conductances of several neurotransmitters (Conway et al., 1988; Svirskis & Hounsgaard, 1989; MacLean et al., 1997; Perrier & Cotel, 2008). Histamine is known to inhibit high voltage-activated calcium channels that, in turn, could inhibit the activation of calcium-dependent potassium channels (Takeshita et al., 1998). Thus, the sustained depolarization with repetitive spikes observed from motoneurons in this study it is not likely to involve calcium

conductances. Indeed, histamine inhibits K^+ currents (Starodub & Wood, 2000), as confirmed by a link between wide-spectrum antagonists of K^+ channels and the appearance of sustained depolarization with repetitive spikes on motoneurons (Schwindt & Crill, 1980; Taccola & Nistri, 2006). However, the story is more complex than anticipated. Indeed, it has been reported that the ionic mechanisms underlying the histamine-induced depolarization might be different among distinct motoneuronal populations (Wu et al., 2012). As a matter of fact, we have identified at least two groups of cells in which histamine produces two different levels of excitation. Thus although in our study histamine was able to depolarize all five motoneurons tested with TTX, we cannot rule out the possibility that a subset of motoneurons might be insensitive to histamine (13%, Wu et al., 2012).

In addition, different subtypes of histaminergic receptors with contrasting functional effects may be involved. For example, while the H_1 subtype is mainly responsible for the blockage of potassium channels associated with an increase in membrane input resistance, H_2 receptors activate I_h channels, producing a decrease in membrane input resistance (Wu et al., 2012). This balanced equilibrium between two opposite factors elicited by distinct receptor subtypes might support the lack of changes in MN input resistance during histamine plus TTX reported in the present study.

About a third of the motoneurons in the current study displayed sustained depolarization, while the others showed a partial repolarization after few minutes of histamine application. Why some motoneurons did not show any sustained depolarization is unclear, but could be related to different kinds of ionic conductances shown by different types of motoneurons (Hounsgaard & Kiehn, 1989). Moreover, the presence of sustained depolarization with repetitive spikes on motoneurons was not necessarily related to the functional significance of recorded motoneurons, since both mainly flexor (L1-L2; Kiehn and Kjaerulff, 1996) and mainly extensor (L4-L5; Kiehn and Kjaerulff, 1996) motoneurons showed this behavior. Proportions of motoneurons with or without

sustained depolarization in this study are comparable to those reported in other studies (Perrier & Hounsgaard, 2003; Bouhadfane et al., 2013). Yet, it remains to be determined if there are differences in how histamine modulates motoneuron output and spinal activity in the developing vs. mature spinal cord.

Application of histamine resulted in generation of complex rhythmic activity recorded from motor pools. This rhythmic activity was characterized by a sustained depolarization, high-frequency tonic activity (of a glutamatergic nature), with synchronous activity among all VRs; and sporadic, slower depolarizing bursts that sometimes lead to the appearance of brief, superimposed epochs of alternating FL cycles. The transient repolarization of VRs, along with changes in rhythmic discharges despite the continuous presence of histamine, is consistent with the observation that only half of motoneurons respond to the agent with a sustained depolarization and high frequency firing. Finally, the increased spontaneous activity after washing out histamine might putatively originate from a rebound of histamine's inhibitory tone on spinal networks, in line with the slowing down of FL, until suppression, evoked by increasing concentrations of the agent. Complexity of rhythmic activity may reflect different responses generated by histamine on different groups of motoneurons and modulation of interneurons of the spinal locomotor circuits responsible for alternated rhythmic activity (Bonnot et al., 1998; Whelan et al., 2000). Notably, histamine slows down the rhythm of the fictive locomotion induced by NMDA and 5-HT. This result is in accordance with the decreased polysynaptic reflex and lower frequency discharge of tonic activity from VRs, but somehow in contradiction with the increased excitability of spinal motoneurons. Indeed, recently, it has been reported that a motoneuronal depolarization increases the locomotor rhythm (Falgairolle et al., 2017). Overall, histamine reduces rhythm, despite augmenting excitability of motoneurons, thus suggesting that premotor interneurons are also modulated by histamine.

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Apart from the multiple well-known functions of histamine (Passani et al., 2007), our results reveal a new role for histamine in locomotor control. Patterns of spinal activity implicated in overground walking seem to be affected by histamine: motoneuron sustained depolarization required for standing posture, modulation of afferent inputs coming from the periphery, and facilitation of interneuronal spinal circuits for the rhythmic and alternated activation of limbs. These different tasks might be controlled by an orchestrated activation of different receptor subtypes and, probably, the relevance of each different histamine receptor varies with the state of spinal network activation (Fidelin et al., 2015).

Implications

Within the complex molecular and cellular milieu that follows a traumatic spinal lesion, increases in the extracellular concentrations of biogenic amines, such as histamine (up to 0.9 µg/L; Kuruvilla et al., 1985), represent a relevant, and to a certain extent underestimated, neuromodulatory factor. Histamine concentrations stabilize at high levels for hours after spinal trauma, at both the injury site and adjacent segments (Naftchi et al., 1974; Kobrine & Doyle, 1976; Kuruvilla et al., 1985; Panneerselvam et al., 1989). Histamine is one of the most potent endogenous vasodilators of the CNS (Burn and Dale, 1926) and contributes to development of hyperaemia and edema (Kobrine & Doyle, 1976; Kobrine et al., 1976a, 1976b; Winkler et al., 1995). An additional effect of increased histamine levels is the progressive permeability of the blood-brain barrier that activates a positive feedback loop and thus promotes a further increase in the amount of histamine that “leaks” into the central hemorrhagic lesion (Gross et al., 1981; 1982; Sharma et al., 2006). After spinal trauma, the first surgical procedures - such as anesthesia, laminectomy and decompression - have been shown to increase spinal levels of histamine within the first 5 hrs (Naftchi et al., 1974; Kuruvilla et al., 1985; Panneerselvam et al., 1989). In the future, it would be important to assess whether and to what extent increased levels of histamine to which

the spinal cord is exposed beyond the acute phases of the trauma may contribute to the transient depression of spinal reflex activity (spinal shock; Ditunno et al., 2004). Moreover, it is important to understand if, in the chronic phase, spared descending histaminergic pathways can directly alter excitability and plasticity of spinal interneuronal networks (Edgerton et al., 2004).

We therefore suggest that in addition to its role in sensory processing and wound healing, modulatory effects on spinal motor systems be considered as a possible contributor to the effects of histamine in vivo. For instance, as therapeutic drugs (including those acting at histaminergic receptors) may be developed to reduce pain (Muthuraman et al., 2014) following a spinal cord injury, it will be important to uncover how they interact with neural networks in the ventral spinal cord that are important for functional motor recovery .

Conflict of interest: no conflicts of interest to declare

Acknowledgments

We are grateful to Prof. Laura Ballerini, Dr. Alessandra Fabbro and Elisa Ius for the excellent assistance in preparing the manuscript. GT is supported by funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie (grant agreement No 661452). HES was supported by NIGMS P20GM103408.

Authors' contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, G.T.; Methodology, G.T.; Investigation, T.C., G.D'A. and G.T.; Formal Analysis, T.C., G.D'A. and G.T.; Writing - Original Draft, T.C., G.D'A., M.R.B., H.E.S, and G.T.; Writing - Review & Editing, M.R.B. and G.T.;

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Visualization, G.D’A. and G.T.; Supervision, M.R.B. and G.T.; Funding Acquisition, M.R.B. and G.T.

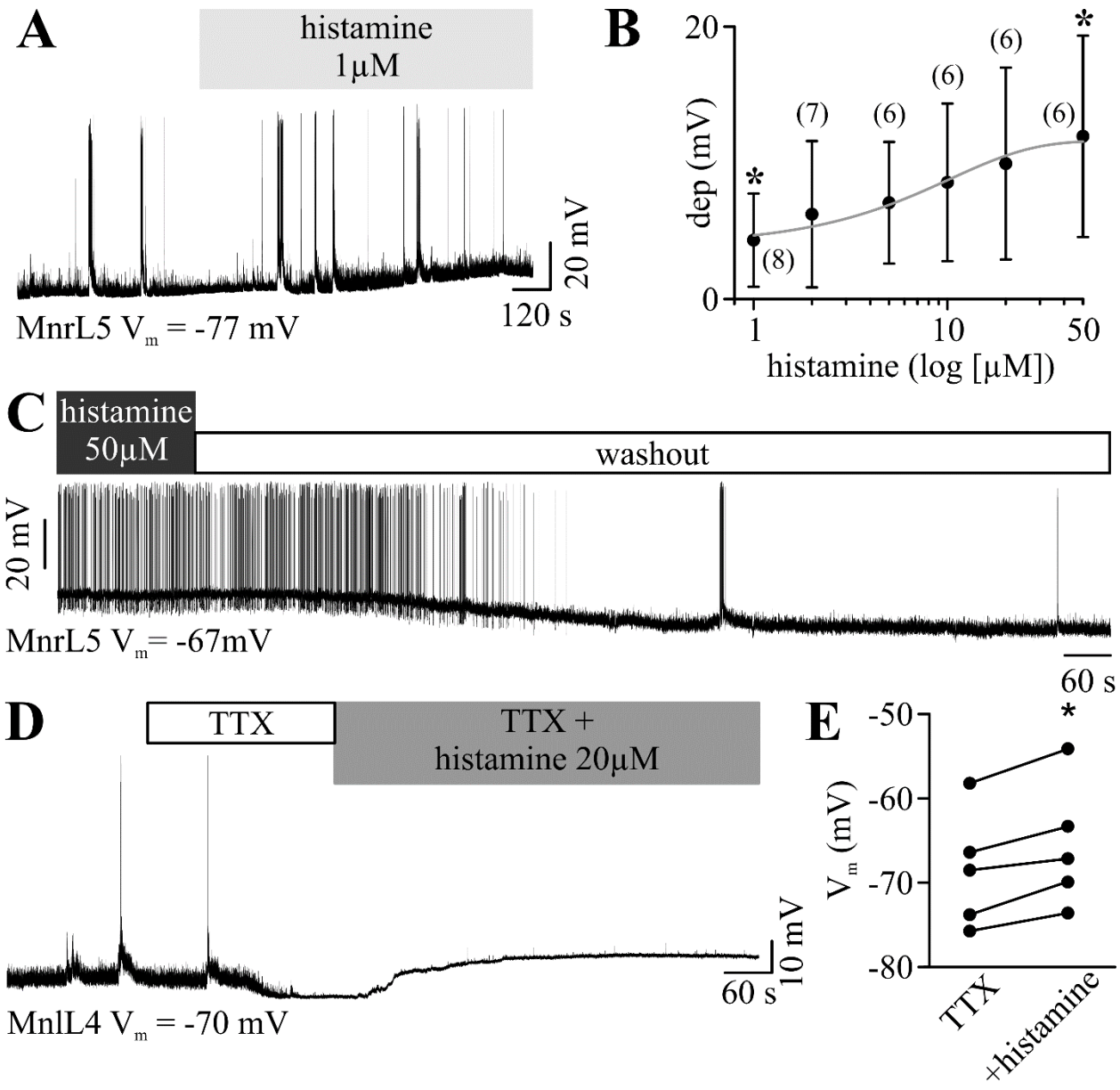


Figure 1. Histamine dose-dependently depolarizes motoneurons, by acting on motoneuronal receptors. A.) After 257 s of perfusion, 1 µM histamine depolarizes lL5 motoneuron (ΔV = 5.65 mV from the initial resting potential, V_m, pair to -67 mV). B.) Dose-response curve for pooled motoneurons fitted to cumulative increments of histamine concentration. Cells are depolarized in a dose-dependent manner with a mean E_{50} value of 8.14 µM. Statistical difference is reached between the lowest and the highest concentrations (*, t-test;

P = 0.023; n = 6 - 8; see values in Table 1). C.) A sustained depolarization with superimposed intense firing induced by histamine (50 µM) on a single rL5 motoneuron fades away after 484 s of subsequent washout in krebs solution. Firing progressively disappears while baseline returns to control values and the effect of histamine is completely reversed after 8 minutes of wash. Initial resting potential (V_m) is -67 mV. D.) A single lL4 motoneuron is exposed to tetrodotoxin (TTX, 1 µM), which hyperpolarizes the cell (-3.66 mV) by completely suppressing firing and spontaneous post-synaptic potentials. Following addition of histamine (20 µM) the motoneuron is depolarized (2.14 mV), even in the continuous presence of the synaptic transmission blocker (TTX, 0.5 µM). Initial resting potential (V_m) is -70 mV. E.) Plot of data from different experiments indicates that histamine (20 µM) during TTX perfusion significantly depolarizes single motoneurons (*, paired t-test, t_4 = -5.648, P = 0.005, n = 5). Note that A, C, D, traces are from different cells.

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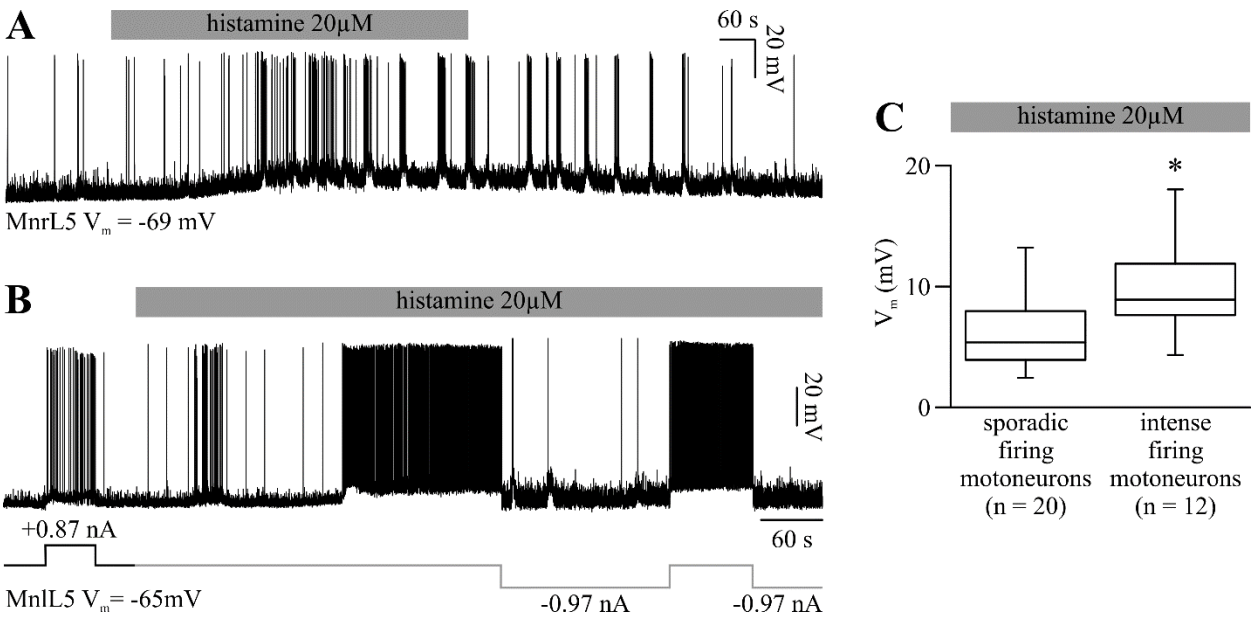


Figure 2. A single application of histamine reveals two types of responses from motoneurons.

A.) 20 µM of histamine (grey upper bar) applied to a motoneuron (right side, lumbar 5 level) evokes a first peak of depolarization (12.42 mV) after a couple of minutes, that, after 10 minutes, repolarizes to 6.35 mV with superimposed sporadic firing. Initial resting potential (V_m) is -69 mV. B.) A long recording from a single lL5 motoneuron (initial resting potential, $V_{m,}$ is -65 mV) shows the appearance of a sustained depolarization and intense firing activity (1.37 Hz mean frequency; left) when manually depolarized (4.27 mV) by injecting current through the microelectrode. After 181 s, the application of histamine (20 µM, upper gray bar) evoked an even higher depolarization (13.21 mV) with more intense firing (3.20 Hz mean frequency), which is transiently switched off when the cell is manually hyperpolarized to resting value (-65 mV; middle-right). Note that A and B traces are from different cells. C.) The box plot quantifies the statistically different depolarization induced by histamine (20 µM) on motoneurons that show sporadic vs. intense firing activity (*, t-test; t_{30} = -3.472, P = 0.002; n = 20, 12).

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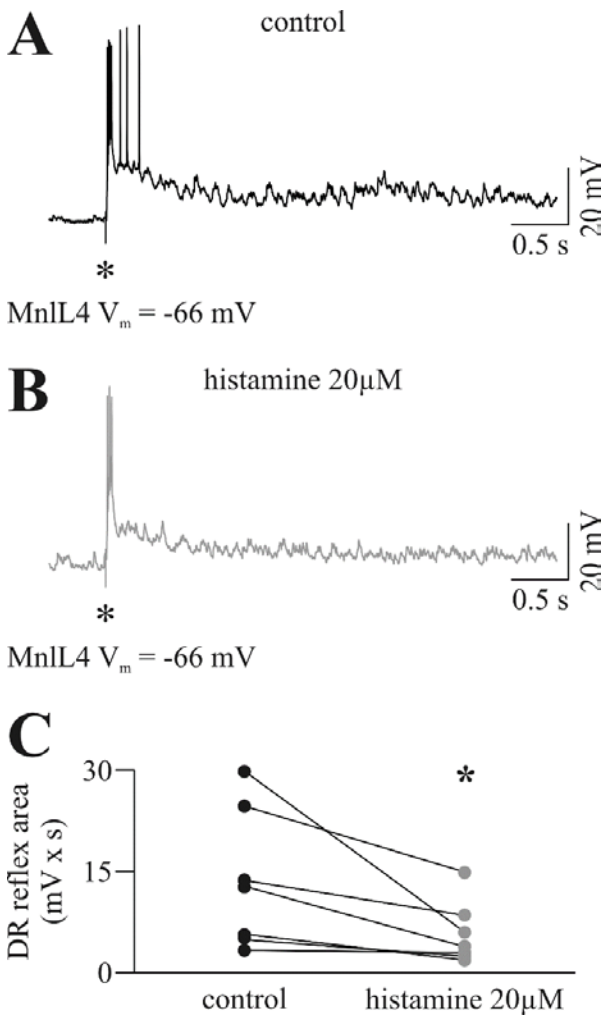


Figure 3. Histamine reduces reflex responses in motoneurons. A.) A single reflex recorded from a rL4 motoneuron and elicited by single electrical pulses (asterisk) applied to DRlL5 (duration = 0.1 ms; intensity = 15 µA, 1.5 Th) is composed of a first peak (mainly due to the monosynaptic transmission from the afferents) and a polysynaptic response with cumulative depolarization and multiple spikes. Initial resting potential (V_m) is -66 mV. B.) After 20 min of histamine (20 µM) application, the cell is manually repolarized (4.03 mV) to resting baseline potential (-66 mV). Now, by delivering the same electrical stimulus, the amplitude of the first peak is unchanged, while only a smaller polysynaptic response with merely few action potentials appears. C.) DR reflex areas show that control values are significantly decreased by 20 µM histamine (*, paired t-test, t_6 = 2.627, P = 0.039; n = 7).

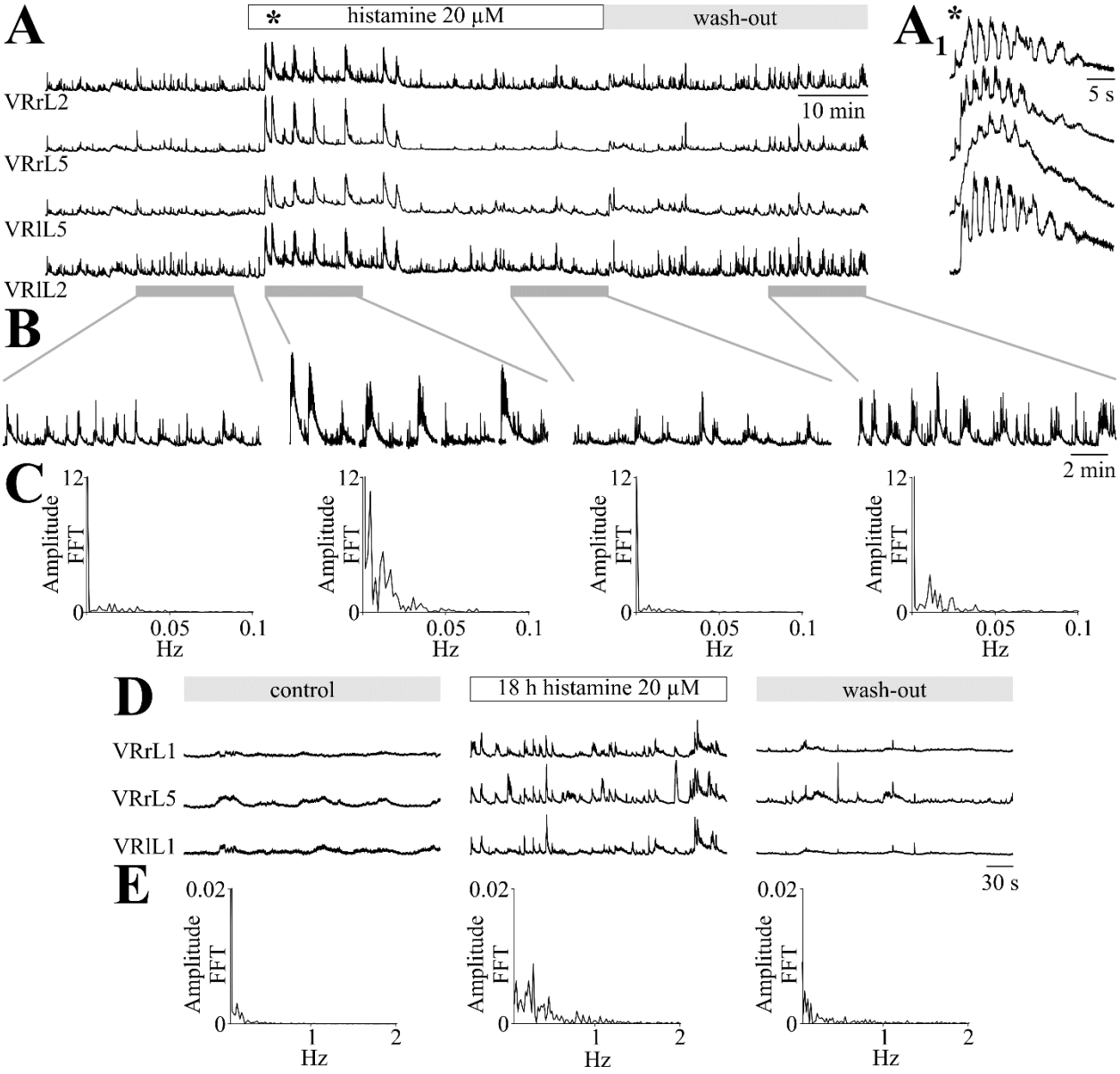
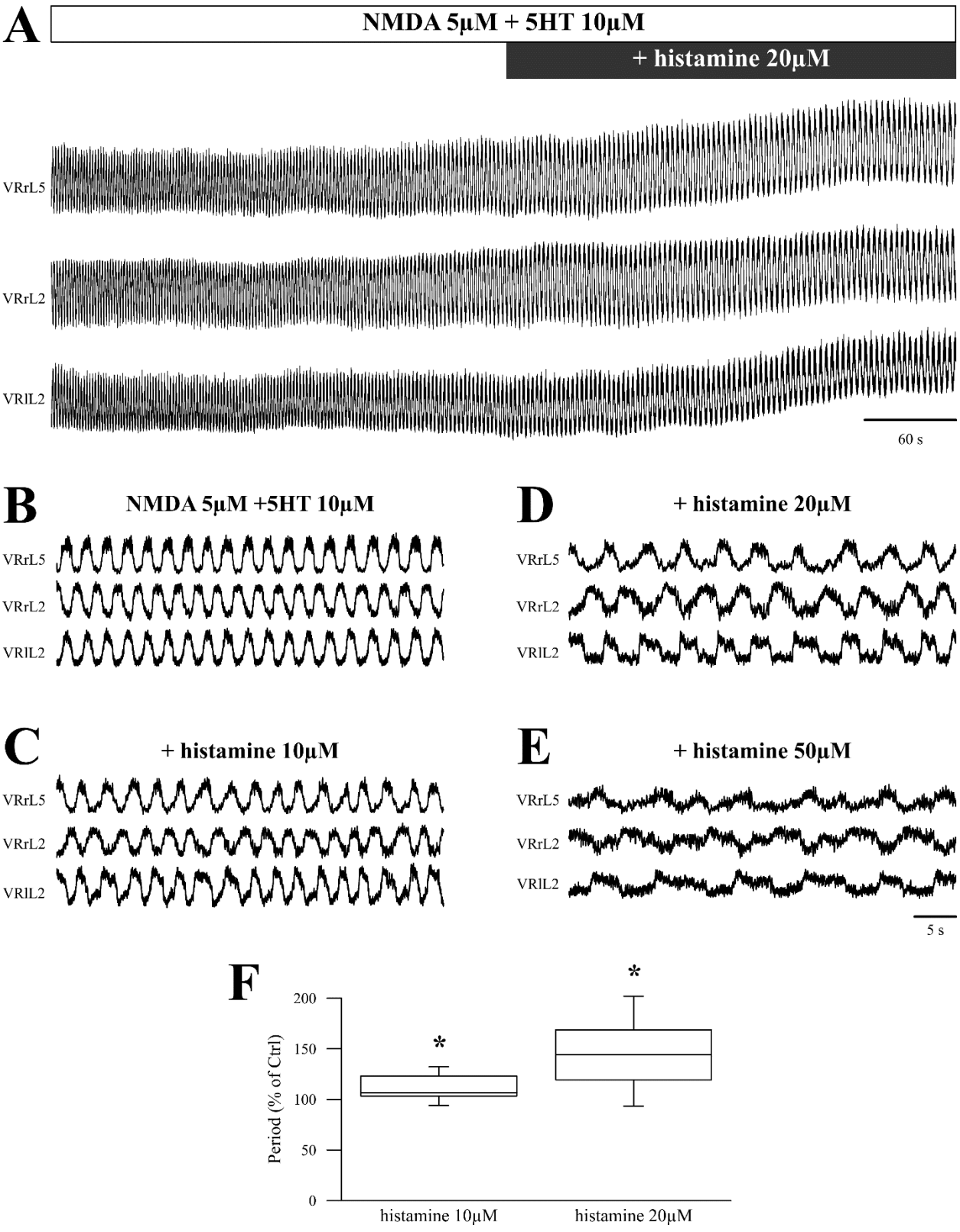


Figure 4. Dynamics of rhythmic discharges induced by histamine on VRs. A.) Continuous recordings taken from contralateral L2-L5 VRs illustrate spontaneous activity during acute and during long application of histamine (20 µM; total duration = 50 min). VRs initially are steadily depolarized (596 µV), with the appearance of superimposed slow burst synchronous activity among VRs. In the continuous presence of the agent, VRs repolarize to 178 µV and bursts spontaneously vanish after about 20 min. A rebound in frequency and amplitude of rhythmic discharges appears in the following washout phase. A_1.) A single burst induced by early histamine

(see star in A) is shown at higher magnification, revealing the internal structure of bursts, each composed of intraburst locomotor-like oscillations ($CCF_{homosegmental}$ = -0.68; $CCF_{homolateral}$ = -0.92). B.) 15 min-long samples are taken from VRlL2 trace in correspondence to the grey rectangles in A, showing at higher magnification the dynamics of rhythmic activity. Corresponding power spectrum analysis was performed to quantify that in control (C., first panel) the main slow frequency was detected at 0.013 Hz, which corresponds to spontaneous tonic activity. During early application of histamine (C., second panel), the main component shifted to 0.005 Hz, in line with the inception of bursting activity. Then, the main component (0.008 Hz) returned to baseline values (C., third panel), and reached 0.011 Hz after washout (C., fourth panel). D.) After recording baseline values (left), the spinal cord was incubated overnight with 20 µM histamine. Following 18 hours of histamine perfusion, spontaneous activity with bursting was recorded (middle). After extensive washout (40 min), traces recovered to baseline (not shown), bursting activity was abolished, and tonic activity was largely suppressed. E.) Power spectra illustrates the increase in the main frequency content of spontaneous activity during baseline (left, 0.055 Hz) and after long application of histamine (middle, 0.275 Hz), that eventually waned after washout (right, 0.037 Hz).


A
NMDA 5µM + 5HT 10µM
+ histamine 20µM
VRrL5
VRrL2
VRlL2
60 s
B
NMDA 5µM +5HT 10µM
VRrL5
VRrL2
VRlL2
C
+ histamine 10µM
VRrL5
VRrL2
VRlL2
D
+ histamine 20µM
VRrL5
VRrL2
VRlL2
E
+ histamine 50µM
VRrL5
VRrL2
VRlL2
5 s
F
Period (% of Ctrl)
200
150
100
50
0
*
*
histamine 10µM
histamine 20µM

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Figure 5. Histamine modulates spinal locomotor activity. A.) A stable fictive locomotion (FL) rhythm, with its characteristic alternation between the left and right sides of the cord and between flexor and extensor motor pools, is induced by bath application of NMDA (5 µM) and 5HT (10 µM). Addition of histamine (20 µM) depolarizes VRs, slowing down frequency of locomotor-like oscillations. B-E.) By applying increasing concentrations of histamine (10, 20, 50 µM), the frequency of alternating discharges is progressively reduced, until a near complete suppression occurs at 50 µM histamine (right panel). F.) Histamine significantly increased the period of the locomotor rhythm at both 10 µM and 20 µM (* vs. control, one-way ANOVA on raw data followed by all pairwise multiple comparison procedures with Tukey Test, $P < 0.001$; $n = 35, 8, 28$).

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