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Research report

Endogenous dopaminergic modulation of the lamprey spinal locomotor network

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Abstract

The lamprey spinal cord contains three dopaminergic systems. The most extensive is the ventromedial plexus in which dopamine is co-localized with 5-HT and tachykinins. In this study we have investigated the effects of endogenously released dopamine on NMDA-induced spinal activity, and for comparison applied dopamine exogenously. The dopamine reuptake blocker bupropion increases the levels of extracellular dopamine in the spinal cord. Bath application of bupropion during ongoing NMDA-induced network activity (around 2 Hz) resulted in an initial increase of the burst rate followed by a transitional phase with the fast rhythm superimposed on a much slower ventral root burst activity (below 0.25 Hz). Finally only the slow rhythm was observed. The same response pattern with regard to the fast and slow rhythms was observed when dopamine was slowly perfused over the spinal cord, resulting in a gradual build-up of dopamine concentration. At low constant dopamine concentrations, however, an increased burst frequency was maintained, but at somewhat higher concentrations the fast burst rate instead was decreased. The degree of modulation of fictive locomotion by dopamine was also tested at low and high NMDA concentrations. Dopamine was found to exert stronger effects at low NMDA concentrations. With high NMDA concentrations dopamine did not induce the transition phase or the slow ventral root bursting. The slow alternating ventral root bursts, induced by bupropion, shifted to synchronized activity when glycinergic synaptic transmission was blocked with strychnine, testifying that the alternation depended on a crossed glycinergic action as previously shown for the fast rhythm.

Theme: Motor systems and sensorimotor integration

Topic: Spinal cord and brainstem

Keywords: Dopamine; Fictive locomotion; Bupropion; *N*-Methyl-D-aspartate; Lamprey

1. Introduction

Modulation of neuronal networks is an important mechanism for adapting the motor pattern to different demands. The lamprey spinal network for locomotion is characterized, and the identity, cellular properties, and synaptic connections of many spinal interneurons and motoneurons are known. However, the interaction between neurons can be modulated to shape behavioral adaptation [5,13,14,16].

Dopamine immunoreactivity is found in cell bodies located around the central canal, and in the lateral part of the grey matter [11,17,19]. Dopamine is also located in a plexus of neurons and processes in the ventromedial part of the spinal cord, into which the dendrites of motoneurons and spinal interneurons project [18,19,22,23]. The aim of this study was to explore the physiological role of dopamine in the control of the locomotor network.

The specific modulatory effects of exogenous dopamine on identified spinal neurons, including Ca^{2+} channel subtypes, and on synaptic transmission within the network and reticulospinal axons, has been investigated in some detail [9,11,18,20,21,24]. Dopamine has a biphasic, concentration-dependent effect on D-glutamate-induced fictive locomotion. Low dopamine concentrations increase, while higher concentrations reduce the frequency of ventral root bursting [11].

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In the ventromedial plexus, dopamine is co-localized with 5-HT and tachykinins [18,22]. 5-HT also reduces the frequency of locomotor activity [7], while substance P potentiates the burst rate [15]. These transmitters also have interacting modulatory effects [20]. In order to investigate the effects of endogenously released 5-HT and substance P, reuptake blockers and peptidase inhibitors, respectively, have been used. The effects were similar to that of exogenous administration of the modulators [3,15].

Bupropion, a dopamine reuptake blocker, increases the extracellular levels of dopamine in the lamprey spinal cord [18,21]. Administration of bupropion to the spinal cord reduces calcium conductances, and thus, the slow afterhyperpolarization (sAHP), in motoneurons and the amplitude of reticulospinal EPSPs via an action on D_2-receptors [18,21].

In this study we have analyzed the effects of administering buproprion on NMDA-induced fictive locomotion and compared them to the effects of a slow exogenous application of dopamine on NMDA-induced fictive locomotion. The results show that endogenously released dopamine has the same modulatory effects over time as bath-applied dopamine on NMDA-induced network activity.

2. Methods

Adult lampreys (*Lampetra fluviatilis*, $n=20$, length of 30 cm) were anaesthetised with tricane methanesulphonate (MS-222, 100 mg/l, Sandoz, Switzerland), and a part of the notocord with spinal cord attached (10–15 segments) from the rostral region was dissected and placed in a cooled (8–12 °C) Sylgard-lined (Sikema, Stockholm) recording chamber (volume, 4.2 ml). The preparation was continuously perfused using a peristaltic pump (0.6 ml/min) with cooled Ringer's containing (in mM): 138 NaCl, 2.1 KCl, 1.8 $CaCl_2$, 1.2 $MgCl_2$, 4 glucose, 2 HEPES, 0.5 L-glutamine, which was bubbled with O_2 and pH adjusted to 7.4 with 1 M NaOH.

Locomotor activity was induced by bath-applied NMDA and ventral root activity was recorded extracellularly with glass suction electrodes. pClamp6 and 8.0 (Axon Instruments, Union City, CA) were used for data acquisition and analysis using a 486 PC-computer equipped with an A/D interface (Digidata 1200, Axon Instruments).

All drugs were dissolved in Ringer's and bath-applied. The following drugs were used: 1–5 μM strychnine (Apoteksbolaget, Sweden), 75–250 μM *N*-methyl-D-aspartate (NMDA, Tocris), 75–200 μM bupropion (RBI), 1–200 μM dopamine (RBI). All solutions containing dopamine were supplemented with L(+)-ascorbic acid (20–30 μM, Merck) to prevent oxidation. Dopamine and bupropion were bath-applied when stable and rhythmic fictive locomotion were obtained.

To quantify the effects of neuromodulators on fictive swimming, ventral root activity was recorded and amplified (bandpass 300 Hz–1 kHz), using a differential AC amplifier (A-M system, Carlsborg, WA, USA) and stored on a PC computer using Clampex 8.0 and analyzed with Clampfit 8.0 (Axon Instruments, CA, USA). Autocorrelations were produced for all raw traces using a custom program (Lorenzo Cangiano) to determine the average cycle period. Traces were analyzed to determine burst frequencies and cycle durations by using 20 consecutive alternating bursts. A power spectrum analysis of rectified ventral root recordings was performed with the fast Fourier transform (FFT) function in Axograph 4.3. This mathematical analysis yields peaks corresponding to the frequencies present in a waveform. A two-way ANOVA showed no significant differences between these three methods for determining burst frequency. Further analysis was performed with Graphpad (GraphPad) and Excel (Microsoft) software. Statistical comparisons were made using Student's *t*-tests for unpaired data. All measurements, unless otherwise stated, are expressed as means±standard error and all *n*-values in the text refer to the number of spinal cords or cells tested.

3. Results

3.1. The dopamine re-uptake blocker bupropion has a biphasic effect on fictive locomotion

To test the effect of endogenous released dopamine on fictive locomotion, the dopamine reuptake blocker bupropion was applied to the entire spinal cord during NMDA-induced fictive locomotion (Fig. 1). The reuptake blocker will produce increased levels of endogenous dopamine at the release site [18].

Bath application of bupropion at the same levels as used in mammalian preparations (75–200 μM, [10,18]) significantly increased the burst frequency of ongoing NMDA-induced (75 μM) fictive locomotion to 130±5% of control after 32±10 min (Fig. 1Ai, 1Aii, B, C, and D; $n=5$ of 5, $P<0.001$). A prolonged application of bupropion induced a transition period in which a rhythm with slower frequency appeared superimposed on the initial fast rhythm (Fig. 1Aiii). The slow rhythm had a frequency of 10±2% of control (Fig. 1B and C; $n=5$ of 5, $P<0.001$). The fast rhythm disappeared 69±17 min after the start of bupropion administration and only the slow rhythm remained (Fig. 1Av, B, C and D). The slow rhythm was very stable and did not vary with time (Fig. 1C).

3.2. Effects of gradually increased dopamine concentrations on fictive locomotion

To investigate if a gradual increase in dopamine concentration could induce a biphasic modulatory effect, as seen with bupropion, a relatively high dopamine concentration (200 μM) was slowly applied to the recording

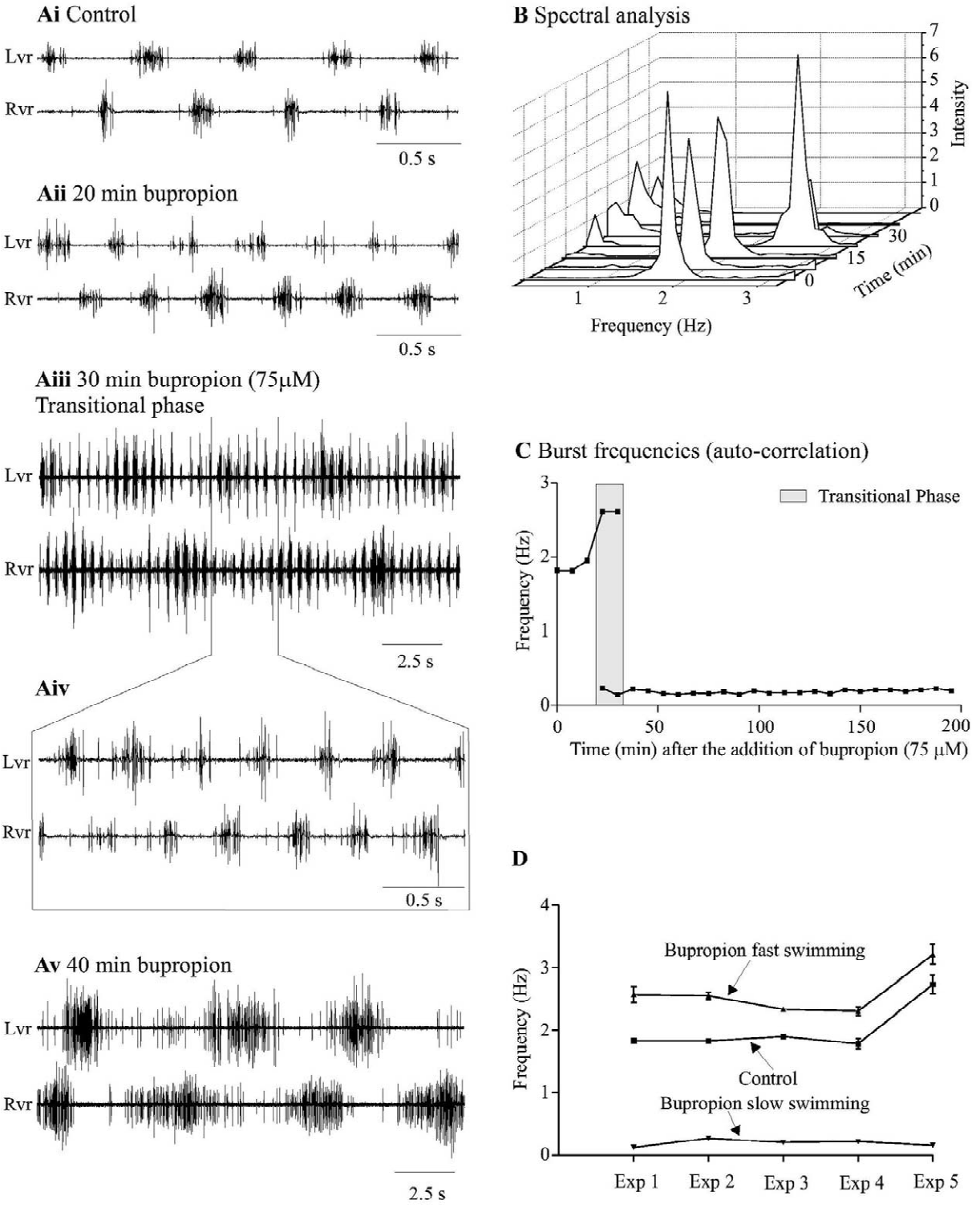

Fig. 1. Effects of bupropion, a dopamine reuptake blocker, on NMDA (75 μM)-induced fictive locomotion. (Ai) Control recording from left (Lvr) and right (Rvr) ventral roots (1.77±0.07 Hz). (Aii) 20 min bath application of bupropion (75 μM) caused a significant increase of the burst frequency (2.31±0.07 Hz). (Aiii) The increase is followed by a transitional phase where a slow frequency modulation can be seen superimposed on the fast rhythm (0.21±0.01 Hz). (Aiv) Expansion of the trace in (Aiii) to show the fast rhythm. (Av) A trace that shows the effect of 40 min bupropion application. The fast rhythm has disappeared and only the slow rhythm remains. (B) A 3-D graph that shows a spectral analysis of the bupropion modulation of fictive modulation. The *z*-axis represents time after addition of bupropion to the bath, the *x*-axis frequency and the *y*-axis intensity. Initially there is a shift to the right indicating an increase in frequency. Subsequently a second peak forms in the low frequency range and both peaks can be seen simultaneously. Finally, only the low frequency peak remains. (C) A graph showing the average burst frequency over time calculated from the auto correlation. (D) A summary graph showing the effects of bupropion in five experiments.

chamber (0.6 ml/min, chamber volume: 4.2 ml) during NMDA-induced (75 μM) fictive locomotion. This will slowly set up a dopamine concentration gradient over time, and it is thus possible to follow the modulatory effects of dopamine until it reaches its maximal effect. Dopamine initially caused a significant increase of the ventral root burst frequency to 140±23% of control after 22±4 min application (Fig. 2Ai, Aii and D, $n=3$ of 4, $P<0.05$). With further dopamine application, the burst frequency entered a transitional phase where a slow ventral root rhythm appeared (9±1% of control, $n=4$ of 4) superimposed on the fast rhythm, the frequency of which still increased

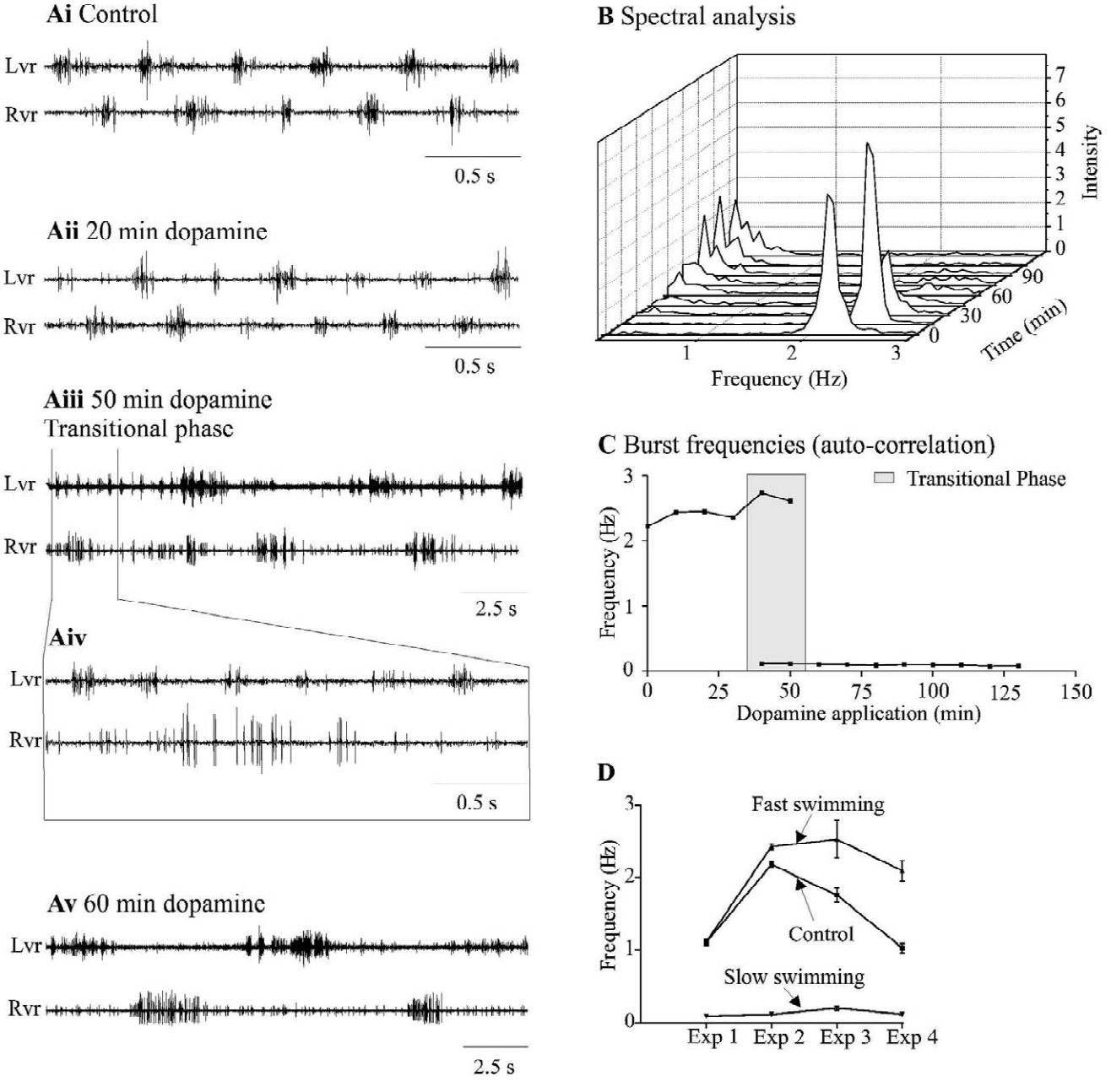

Fig. 2. Effects of gradually increasing dopamine concentrations on NMDA (75 μM)-evoked fictive locomotion. (Ai) Control recordings from left (Lvr) and right (Rvr) ventral roots (2.15±0.04 Hz). (Aii) After 20 min dopamine (200 μM) application there was a significant increase in burst frequency (2.45±0.04 Hz, $P<0.001$). (Aiii) The increase in burst frequency is followed by a transitional phase where a slow burst frequency (0.12±0.01 Hz) is superimposed on the fast rhythm. (Aiv) Expansion of the trace in (Aiii) to show the fast rhythm. (Av) After 60 min of dopamine application the fast alternating rhythm is much reduced while the slow rhythm remains stable. (B) FFT spectral analysis of the modulation of fictive locomotion at gradually increased dopamine concentrations. The *z*-axis represents time after addition of dopamine to the bath, the *x*-axis frequency and the *y*-axis intensity. The fast rhythm was initially increased and subsequently declined, while the slow rhythm progressively increases in intensity. (C) The graph shows the average burst frequency over time calculated from the auto correlation. (D) A summary graph that shows the results from four experiments (initial control, fast swimming rate, and slow rate).

(Fig. 2Aiii, Aiv, B, and C). The fast alternating ventral root rhythm declined, to eventually disappear after the addition of dopamine (54±4 min), whereas the slow alternating ventral root bursts dominated entirely (Fig. 2Av, B, and C). The slow bursts sometimes appeared to be modulated in fast bursts (Fig. 2Av and B) at a low intensity.

Thus, it is possible to obtain both the effects of low and high dopamine concentrations by gradually increasing the dopamine concentrations, and also to induce a transitional phase where a fast and slow rhythm are superimposed on each other.

3.3. The frequency of the fast rhythm is also reduced by dopamine

To investigate the effect of low dopamine concentrations on fictive locomotion with high NMDA concentrations, and to study the effect of dopamine on the fast rhythm, 150–200 μM NMDA was used, while cumulatively increasing the dopamine concentration from 1 to 100 μM. The frequency was increased by application of 1–30 μM dopamine with a peak at 5 μM (Fig. 3A). With dopamine concentrations between 50 and 100 μM the frequency of the fast rhythm was reduced without inducing a slow rhythm (Fig. 3A). These results show that dopamine has a biphasic effect also on the fast rhythm without inducing the slow rhythm. This means that dopamine has two concentration-dependent effects on the fast ventral root bursts: low dopamine concentrations increase the frequency of the fast rhythm induced by high NMDA concentrations, whilst it reduces the frequency of the fast rhythm at high concentrations.

3.4. The effects of dopamine on fictive locomotion are dependent on NMDA-concentration

To investigate if the modulatory effect of dopamine was different at low (75 μM) and high (250 μM) NMDA-concentration, we applied high dopamine concentrations (200 μM) to ongoing fictive locomotion induced by either 75 μM or 250 μM NMDA. When fictive locomotion was induced with 75 μM NMDA, the burst frequency was reduced by 91±5% (Fig. 3B; $n=4$, $P<0.0001$) and the slow rhythm was induced. Dopamine reduced the fast frequency of the ventral root bursts by only 20±1% (Fig. 3B; $n=4$, $P<0.0001$) during swimming induced by 250 μM NMDA, and a slow rhythm was not induced.

These results suggest that the dopamine-induced reduction of the swim frequency is dependent on the strength of the excitatory drive by NMDA. Slow and weak swimming is more sensitive to dopamine modulation, where dopamine induces the slow rhythm. Swimming induced by high NMDA levels is more resistant to dopamine modulation and the slow rhythm is not induced, although the fast frequency is still significantly reduced.

3.5. The alternating ventral root burst during the slow rhythm is shifted to synchronized activity by strychnine

To investigate if the slow rhythm induced by bupropion was dependent on glycinergic synaptic transmission, as in the fast rhythm [4,6], the glycine receptor antagonist strychnine was administered. Bath application of strychnine (1–5 μM) during the slow rhythm did not affect the frequency of the ventral root bursts (Fig. 4A1, $n=3$), but the alternating rhythm between the left and right sides shifted to a synchronized activity (Fig. 4B1). A cross

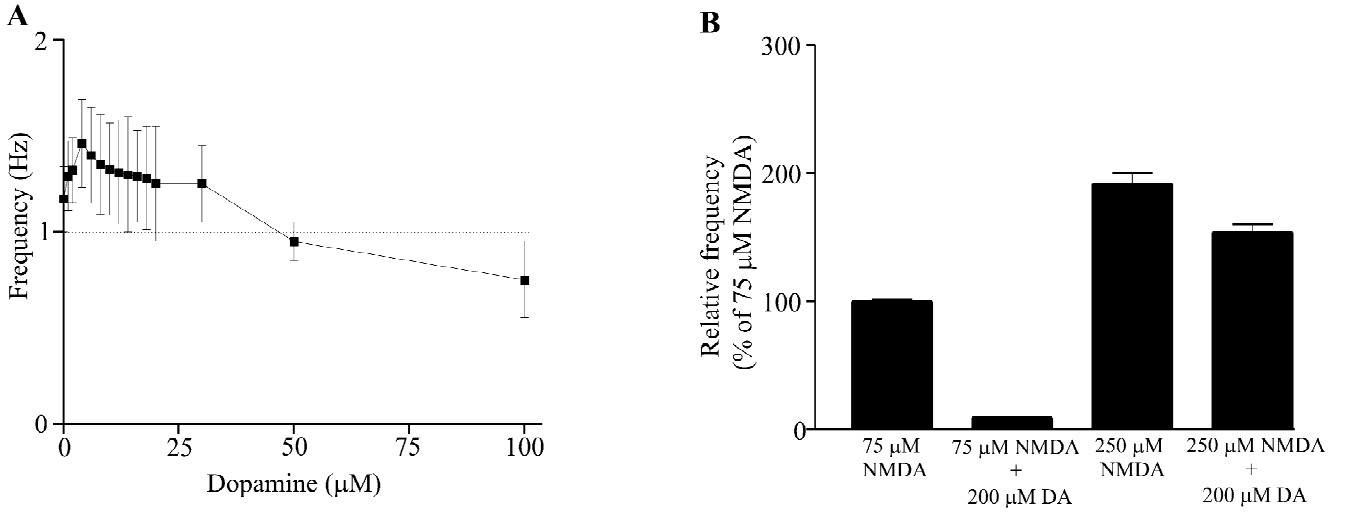

Fig. 3. The modulatory effects of a cumulatively increased dopamine concentration on the fast rhythm (150–200 μM NMDA). (A) 1–10 μM dopamine caused a marked increase of the burst frequency, which became less pronounced when the dopamine level was increased and finally fell below the control burst value. (B) The effects of dopamine (200 μM) at different NMDA concentrations. The frequency of fictive locomotion induced with 75 μM NMDA was reduced by 91±5% by dopamine with an induction of the slow rhythm. When fictive locomotion was induced with 250 μM NMDA the frequency was only reduced by 20±1% by dopamine and a slow rhythm was not induced.

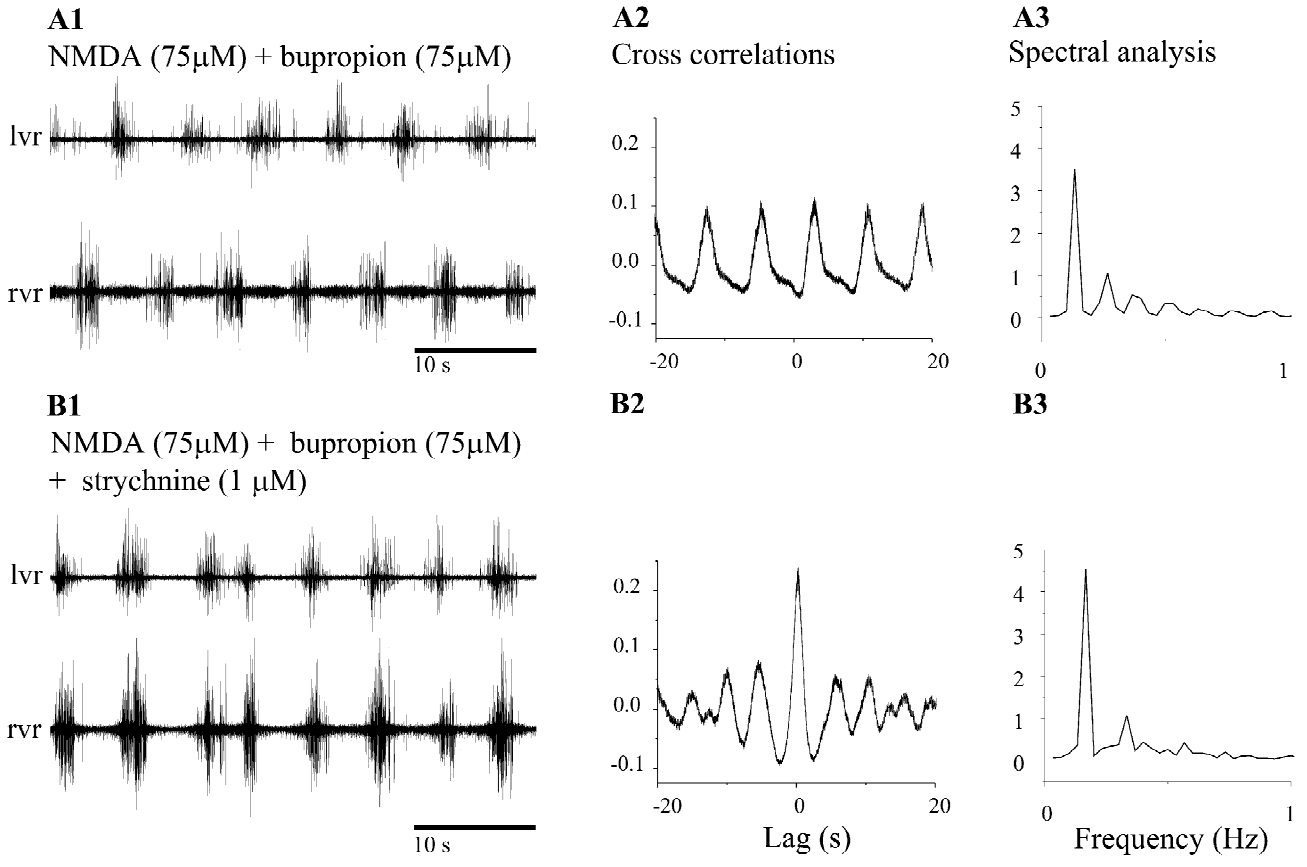

Fig. 4. The effects of strychnine on bupropion induced slow rhythm. (A) Control trace showing the slow rhythm induced with NMDA (75 μM) and bupropion (75 μM). (A1) The slow rhythm was alternating between the left and right sides. A2 shows the cross correlation between left and right ventral roots, and A3 the spectral analysis. (B1) Bath application of strychnine (1 μM) shifts the alternating activity to a synchronous activity without significant effect on the burst frequency. The cross correlation in B2 shows that the pattern of activity is now synchronous. The spectral analysis in B3 shows that the frequency is the same as in A3.

correlation analysis and spectral analysis confirmed the shift from an alternating activity to a synchronized rhythm, without effects on the burst frequency (Fig. 4A2–3 and B2–3). This result shows that the slow rhythm is dependent on glycinergic reciprocal inhibition for generating alternating activity between the left and right side of the cord. It also demonstrates that the burst generation during the slow rhythm is not dependent on glycinergic synaptic transmission.

4. Discussion

The present study shows that endogenous dopamine has the same effect on fictive locomotion as gradually increased exogenous dopamine concentrations. Dopamine has modulatory effects on fictive locomotion depending on dopamine concentration and NMDA concentration. Dopamine has a biphasic effect on the fast rhythm induced by high NMDA levels. Low dopamine concentrations increase the burst frequency but higher concentrations cause a reduction. In fictive swimming induced with low NMDA levels, high concentrations of dopamine cause the fast burst rate to shift to a stable, much slower frequency.

4.1. Bupropion elevates the endogenous dopamine concentration that modulates fictive locomotion

A blockade of the dopamine reuptake by bupropion causes a gradually increasing dopamine concentration. It has the same effects on fictive locomotion and on modulation of cellular properties and synaptic transmission in the lamprey spinal cord as exogenous dopamine [18,21]. The depressive effects of dopamine and bupropion on reticulospinal transmission are blocked by the selective D2-receptor antagonist eticlopride, which shows that the effect seen with bupropion is mediated via a dopamine receptor [21]. This suggests that dopamine is released from dopaminergic spinal neurons during fictive locomotion. It also suggests that these neurons are active during fictive locomotion and may play an intrinsic role in the spinal network for locomotion. Dopamine is co-localized with 5-HT in the ventromedial plexus. The 5-HT reuptake blocker citalopram increases the extracellular 5-HT concentration and mimics the effect of 5-HT on fictive

locomotion by reducing the burst frequency [3]. 5-HT and dopamine thus exert similar effects in reducing the burst frequency of the spinal locomotor network, but 5-HT does not cause the increase in burst frequency seen with low dopamine concentrations and bupropion. The ventral plexus also contains tachykinins that are known to potentiate the frequency of the ventral root bursts, an effect that lasts for over 24 h. The endopeptidase blocker phosphoamidon mimics the effect of bath-applied substance P [15]. These results taken together with those of the present study show that all the three co-localized transmitters are released during fictive locomotion. It also suggests that the activity of the three modulators is regulated by the balance between their release and their reuptake or inactivation systems. This type of regulation would limit the modulatory action both temporally and spatially. Dopamine (60 μM) and 5-HT (100 nM) have additive effects on fictive locomotion in reducing the burst rate [18]. The transmitters actually interact and the induction of the substance P potentiation can be blocked by 5-HT, but not by dopamine [20].

4.2. The action of dopamine on fictive locomotion

A low level of dopamine causes an increased burst rate, both at low and at high levels of NMDA drive. One mechanism that can account for this finding is that dopamine causes a presynaptic depression of crossed glycinergic inhibition [9,11]. A reduction of the crossed glycinergic transmission is known to cause an increased burst rate [6,8,12], and it can thus explain this finding. At higher concentrations, however, the fast rhythm is instead slowed down. This may be explained by the fact that dopamine also causes a reduction in the Ca^{2+} current in the soma of glutamatergic neurones [9,18,24], and thereby indirectly a reduction of the slow afterhyperpolarisation (sAHP) which is due to Ca^{2+}-activated K^{+} channels. A reduction of the sAHP, everything else being equal, will cause a reduced spike frequency adaptation, and thereby also longer bursts and slower swimming [8]. If this effect dominates over the presynaptic effect at higher concentrations, it can explain the bi-phasic effects of dopamine on the fast burst rate.

By gradually increasing the dopamine concentrations either by an uptake blocker or by an exogenous administration during fictive locomotion, induced with low NMDA concentrations, the fast rhythm is replaced by a much slower rhythm (below 0.25 Hz). In a transient phase the fast rhythm is superimposed on the slow bursts. The slow rhythm can also be induced by a longitudinal cut along the midline of the spinal cord [2], which shows that the slow rhythm can be produced by an ipsilateral pattern generator. Strychnine shifted the alternating slow rhythm to a synchronized activity between the left and right sides of the spinal cord without affecting the frequency. A shift to synchronization has previously been shown for the fast rhythm with strychnine [4]. The fact that the frequency was not affected shows that glycine is not required for burst termination during the slow rhythm, but rather that the main function of the glycinergic activity is to coordinate the alternating locomotor activity between the left and right side. The excitatory crossed connections presumably synchronize the activity of both sides after strychnine. The slow ventral root activity may have a role during steering and an alternating rhythm between dorsal and ventral myotomes may also occur [1].

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