Isoflurane Disrupts Central Pattern Generator Activity and Coordination in the Lamprey Isolated Spinal Cord

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**Background:** Although volatile anesthetics such as isoflurane can depress sensory and motor neurons in the spinal cord, movement occurring during anesthesia can be coordinated, involving multiple limbs as well as the head and trunk. However, it is unclear whether volatile anesthetics depress locomotor interneurons comprising central pattern generators or disrupt intersegmental central pattern generator coordination.

**Methods:** Lamprey spinal cords were excised during anesthesia and placed in a bath containing artificial cerebrospinal fluid and D-glutamate to induce fictive swimming. The rostral, middle, and caudal regions were bath-separated using acrylic partitions and petroleum jelly, and in each compartment, the authors recorded ventral root activity. The authors selectively delivered isoflurane (0.5, 1, and 1.5%) only to the middle segments of the spinal cord. Spectral analyses were then used to assess isoflurane effects on central pattern generator activity and coordination.

**Results:** Isoflurane dose-dependently reduced fictive locomotor activity in all three compartments, with 1.5% isoflurane nearly eliminating activity in the middle compartment and reducing spectral amplitudes in the anesthetic-free rostral and caudal compartments to 23% and 31% of baseline, respectively. Isoflurane decreased burst frequency in the caudal compartment only, to 53% of baseline. Coordination of central pattern generator activity between the rostral and caudal compartments was also dose-dependently decreased, to 42% of control at 1.5% isoflurane.

**Conclusion:** Isoflurane disrupts motor output by reducing interneuronal central pattern generator activity in the spinal cord. The effects of isoflurane on motor output outside the site of isoflurane application were presumably independent of effects on sensory or motor neurons.

The immobilizing potency of anesthetics is determined by the minimum alveolar concentration (MAC) needed to block gross and purposeful movement in response to a supramaximal noxious stimulus. This endpoint is defined by the abolition of organized movements involving multiple limbs, head turning, or both.1 Spinal sites of action for the immobilizing properties of anesthetics are more sensitive than supraspinal sites,2–5 although supraspinal immobilizing effects can vary depending on which anesthetic is used.2,6 Several studies have shown that volatile anesthetics depress spinal sensory7–11 as well as motor neurons.12–14 However, no studies have investigated general anesthetic effects on the activity and intersegmental coordination of spinal interneuronal locomotion-generating circuits, known as central pattern generator (CPG) neurons.

The lamprey has been used extensively as a model vertebrate locomotor system that shares many anatomic, functional, and pharmacologic properties with that of mammals.15,16 Because of the unique advantages provided by the lamprey preparation, we have a relatively better understanding of the neural circuitry underlying lamprey locomotion and its modulation. The lamprey isolated spinal cord preparation might therefore serve as a useful tool for the study of anesthetic immobilizing actions. The lamprey spinal cord, having a diameter of only approximately 200 μm, is avascular and normally receives nutrients and oxygen from the cerebrospinal fluid.17 Experimentally, this permits the excised spinal cord to be readily accessed by gases, nutrients, and drugs using superfusion with artificial cerebrospinal fluid (aCSF). It is also possible to bath-separate the spinal cord18,19 so that anesthetics can be selectively delivered to specific spinal regions. Furthermore, a previous lamprey study has shown that clinically relevant concentrations of halothane cause immobility and depress spinal sensory neurons.20 Taken together, the lamprey isolated spinal cord preparation seems to be applicable as a model for the study of anesthetic effects on spinal locomotor circuitry.

Lamprey swimming behavior is characterized by stereotyped, left–right alternating rhythmic contractions of axial musculature in each segment, traveling in a rostro-caudal wave such that a constant intersegmental phase lag is maintained across swimming speeds.21 This phase constancy requires intersegmental coordination, which is orchestrated through ascending and descending coupling of segmental CPG neurons.22–24 A stable and prolonged locomotor rhythm is elicited by application of glutamate agonists to the isolated spinal cord. In this preparation, all of the musculature is removed, thus eliminating the ability for actual movement. However, “fictive” swimming is observed by recording ventral root activity, the pattern of which progresses rostrocaudally along spinal segments and is nearly identical to that observed in vivo.25

We induced fictive swimming in the lamprey by bath application of D-glutamate to the isolated spinal cord, and selectively applied isoflurane to the middle third of the excised spinal cord while recording ventral root...
activity in the rostral, middle, and caudal thirds. We hypothesized that clinically relevant concentrations of isoflurane would disrupt rhythmicity and intersegmental coordination of motor output in spinal regions that lie outside the intervening segments receiving isoflurane. This result would suggest that volatile anesthetics such as isoflurane depress CPG activity and coupling at anesthetic concentrations that disrupt movement coordinated across multiple spinal segments.

Materials and Methods

The University of California, Davis, Animal Care and Use Committee approved this study. Lamprey were housed in fresh water maintained at 4°C. Ammonia concentrations and pH were checked weekly, and the tank water was changed when necessary.

In Vivo Determination of Isoflurane EC\textsubscript{50} for Immobility

In an initial in vivo pilot experiment, the EC\textsubscript{50} for immobility was determined on two adult silver lamprey (Ichthyomyzon unicuspus) by delivering a 60-mA, 100-Hz electrical stimulus to the distal 3 cm of the tail. The stimulating electrodes consisted of two metal prongs that were spaced apart far enough to contact both sides of the tail and gently secure the animal’s tail against the bottom of the glass chamber. Isoflurane in 100% O\textsubscript{2} was bubbled into 3 l of 7°–10°C fresh water in a glass chamber that contained a lamprey. After a 20-min equilibration time, the tail stimulus was delivered for up to 1 min. Swimming away from the stimulus was considered a positive movement response. Isoflurane concentration was increased or decreased by 0.2%, depending on the response, and the average of the concentrations that just permitted and just prevented movement was taken as EC\textsubscript{50}.

Isolated Spinal Cord Preparation

Isolated spinal cord experiments were conducted on eight lamprey. Animals were anesthetized with tricaine methanesulfonate (Sigma, St. Louis, MO) and decapitated. A 45- to 50-segment section of the spinal cord (spanning from the most caudal gill hole to the anus) was excised and placed into a bath, which was then separated using notched acrylic dividers that were sealed around the spinal cord and walls of the bath with petroleum jelly. The rostral and caudal thirds of the spinal cord were superfused separately from the middle third. A conduit linked the flows to the rostral and caudal compartments of the bath. The perfusion system for the middle compartment had an isoflurane (ISO) vaporizer in line with the gas flow to permit delivery of isoflurane to the middle compartment only (shaded region), while one ventral root (VR) was recorded in each compartment.

three compartments. The D-glutamate concentration was always the same for all compartments. Before data collection, we increased the D-glutamate concentration in 0.1- to 0.2-mM increments until we observed stable fictive locomotion in all compartments.

We used saline-filled silver wire suction-pipette electrodes to record from three ventral roots simultaneously (one in each compartment). Raw ventral root activity was amplified using digital amplifiers from Tucker-Davis Technologies (Alachua, FL) and digitally acquired on a personal computer at a 4-KHz sampling rate using a CED power 1401 and spike 2 software (Cambridge, England). Under control conditions, a mixture of 95% oxygen and 5% carbon dioxide was bubbled into two 2-l flasks filled with aCSF and then delivered to each compartment via a roller pump at a flow rate of approximately 50 ml/min. The roller pump worked two separate channels of flow, one for the middle compartment that received isoflurane and one for the rostral and caudal chambers (connected by a stainless steel conduit) that did not receive isoflurane. The overflow was suctioned off and returned to the flask. After collecting 10–15 min of baseline data, isoflurane (0.5, 1, or 1.5%) was bubbled into the flask supplying the middle compartment. Gas-phase isoflurane concentration in the flask was monitored using an Ohmeda Rascal II agent analyzer (Helsinki, Finland). After a 20-min equilibration period, data were collected for at least 6 min. Anesthetic concentrations were delivered in mixed order from experiment to experiment, and at
least two recovery periods (lasting at least 30 min) elapsed between changes in isoflurane concentration.

Gas Chromatography
Aqueous-phase isoflurane concentrations were measured from the aCSF in the bath using a Varian gas chromatograph (model 3900; Walnut Creek, CA) and methods modified from previously published protocols. In brief, 1-ml perfusate samples were taken from each compartment under control conditions and 20 min after changes in isoflurane concentration. Samples were added to 1 ml of a chloroform extraction solution containing methylene chloride (250 μg/ml), which was used as an internal standard. Chromatographic separation was performed using a 30 m × 0.53-mm-ID Crossbond® 100% dimethyl polysiloxane megabore capillary column (Rtx®-1; Restek, Bellefonte, PA). In a pilot experiment, we compared aqueous isoflurane concentration in the bath with that in the flask that supplied the bath and found that mean isoflurane bath concentrations were 98.6 ± 1.6% of the flask concentration, indicating that little, if any, isoflurane escaped from bath aCSF into the air above.

Data Analysis
The last 6 min of data were analyzed for each condition. Spike times were acquired from raw ventral root activity by setting a spike threshold of 1.5 times the noise level. The spike times for each of the three channels were then entered into the commercial spike analysis program Neuroexplorer (Nex Technologies, Littleton, MA). Using these spike times, power spectra were generated from ventral root activity for all three compartments. To quantify motor coordination between the rostral and caudal compartments, spectral coherence of ventral root activity was calculated for each anesthetic condition. Simply stated, spectral coherence was used as a measure of intersegmental coordination, or correlation of activity between two ventral roots, which is calculated by the ratio of the cross-spectrum (between two channels) to the autospectrum (within channel). The resulting ratio of the cross-spectrum to the autospectrum yields a coherence value between 0 and 1, where a value near 1 indicates that the activity of the two channels is highly correlated (entrained to the same rhythm), and a coherence value near 0 indicates that the activity is uncorrelated (exhibits a high degree of independent bursting).

To generate power spectra from ventral root activity, the software divides the data into multiple time windows and performs a fast-Fourier transform (FFT) on each window (a total of 13 in this study) and averages the FFTs across windows. Thus, if a ventral root exhibits bursts of activity once per second, the power spectrum for that root will contain a peak at 1 Hz. For each ventral root (rostral, middle, and caudal) in each animal, power spectra across anesthetic conditions and recovery were normalized to percent peak spectral amplitude of the baseline (no isoflurane) condition.

To determine coherence, the program windows the signal and performs an FFT on each window, as above for the power spectra, and calculates coherence using the formula
\[
C_{RC} = \frac{(P_{RC}^2)}{(P_{RR} * P_{CC})},
\]
where \(C_{RC}\) is the rostrocaudal coherence value between rostral and caudal ventral root activity (R and C). The cross-spectrum, \(P_{RC}\), is calculated by taking the product of each R and C FFT in each time window and averaging them across windows. The autospectrum, \(P_{RR}\) and \(P_{CC}\), is calculated by taking the square of each window’s FFT and averaging them for each respective channel.

The 99% confidence interval (CI) for coherence may then be calculated according to Rosenberg et al.: \(^{28}\)
\[
CI = 1 - (1 - \alpha)\frac{1}{L - 1},
\]
where \(\alpha\) is the confidence level (0.99, or 99% in the current study), and \(L\) is the number of windows the signal has been divided into for coherence analysis.

Peak spectral amplitudes, burst frequency (determined by the frequency at peak spectral amplitude), and peak spectral coherence were each analyzed using a two-factor analysis of variance (animal × anesthetic condition), followed by post hoc Tukey multicomparison tests. A \(P\) value less than 0.05 was considered statistically significant.

Results
Gas Chromatography Analysis of Bath Isoflurane Concentrations
In a pilot experiment, isoflurane concentrations in the lamprey bath were measured by gas chromatography analysis and were found to have a good correspondence to those concentrations monitored by the agent analyzer from the flask that delivered the lamprey aCSF to the bath (fig. 2). Samples taken from the middle compartment during each experiment had mean isoflurane concentrations of 72.6 ± 5.8, 102.9 ± 6.5, and 150.1 ± 11.5 μg/ml when 0.5, 1.0, and 1.5% isoflurane were delivered to the reservoir flask containing lamprey aCSF solution. No detectable level of isoflurane was present in samples taken from the rostral or caudal compartments (detection threshold < 0.2 μg/ml).

In Vivo Determination of Isoflurane EC\(_{50}\)
The isoflurane EC\(_{50}\) value for both intact lampreys was 1.2%, corresponding to an aqueous concentration of approximately 116 μg/ml (fig. 2).
Fictive Swimming

Under baseline conditions, the spinal cord displayed a fictive swimming pattern in response to D-glutamate (fig. 3A), exhibiting rhythmic ventral root activity at a mean burst frequency of 0.60 ± 0.12 Hz, with a mean peak coherence of 0.64 ± 0.21 between the rostral and caudal compartments.

Direct Effects of Isoflurane on Ventral Root Activity

Isoflurane, from 0.5 to 1.5%, dose-dependently reduced ventral root activity recorded from the middle compartment that received isoflurane (figs. 3B and C). Mean peak spectral amplitudes were reduced to 15, 5, and 2% of control at isoflurane concentrations of 0.5, 1, and 1.5%, respectively (P < 0.001–0.01). Application of isoflurane to the middle chamber significantly reduced the burst frequency only at the highest isoflurane concentration of 1.5% (P < 0.02), although at this concentration, activity was nearly abolished (figs. 3 and 4).

Indirect Effects of Isoflurane on Ventral Root Activity Outlying the Site of Isoflurane Application

Isoflurane disrupted ventral root activity in the outlying rostral and caudal compartments that did not receive anesthetic. Isoflurane reduced peak spectral amplitude in the rostral compartment to 59, 35, and 25% of control at 0.5, 1, and 1.5% isoflurane, respectively (P < 0.03; figs. 4A and B). Isoflurane also significantly reduced peak spectral amplitude in the caudal compartment to 35 and 23% of baseline at 1.0 and 1.5% isoflurane, respectively (P < 0.03). Isoflurane did not significantly affect burst frequency in the rostral compartment but significantly reduced burst frequency in the caudal compartment, from 0.60 ± 0.14 Hz to 0.32 ± 0.29 Hz at 1.5% isoflurane (P < 0.02; fig. 4C).

Isoflurane significantly reduced mean peak coherence between ventral root activity in the rostral and caudal compartments, from a mean baseline value of 0.64 ± 0.21 to 0.43 ± 0.16 and 0.26 ± 0.04 at 1 and 1.5% isoflurane, respectively (P < 0.02). An individual example showing isoflurane-induced reduction in coherence is shown in figure 5A, and mean effects are shown in figure 5B.

Discussion

The current data confirm previous reports suggesting that isoflurane can act to block organized movement largely by action within the spinal cord and provide novel findings to suggest that a significant amount of this depression results from anesthetic action on interneurons that participate in spinal locomotor networks.

The Lamprey as a Model for Vertebrate Locomotor Systems

The extensive use of the lamprey and a relatively thorough understanding of its locomotor system result from the unique advantages provided by this preparation. First, compared with mammals, there are fewer...
degrees of freedom to account for in lamprey locomotion, which is generated almost entirely by axial musculature. Lamprey swimming behavior is characterized by stereotyped, left-right alternating rhythmic contractions in each segment, traveling in a rostrocaudal direction such that one cycle period, or wave, is maintained along the lamprey’s body length across a range of swimming speeds. Because there are approximately 100 spinal segments, this requires an intersegmental phase lag of approximately 1% of the cycle period. Another advantage to this preparation is that application of excitatory amino acid agonists to the isolated spinal cord produces a “fictive” swimming pattern, which is stable over long periods of time and nearly identical to that seen in the intact lamprey. In the current experiment, D-glutamate induced stable fictive locomotion consisting of typical intersegmental phase lags of approximately 1% of the cycle period. Figure 3 shows an example of ventral root activity, with a rostral-to-caudal phase lag of 0.53 s, or 30% of the cycle period across 31 segments in this case. These data suggest that sensory and supraspinal commands are not crucial for generating behaviorally appropriate swimming, although these inputs are necessarily capable of modulating the direction and frequency (speed) of the locomotor pattern. A third advantage to using the lamprey preparation is that several classes of interneurons of the locomotor network have been identified and characterized. Using the cellular and intersegmental coupling properties of these neuronal classes, mathematical models have been constructed to simulate the locomotor pattern and its modulation. Last, because the spinal cord can be bath-separated, as in the current study, agents can be selectively delivered to certain spinal segments and not to others to test for effects of these agents on CPG activity and coupling.

**Effects of Isoflurane on Lamprey Locomotor Networks**

Many studies have used spectral analysis as an objective means to quantify a multitude of rhythmic neurophysiologic processes, including motor activity and coordination. We applied spectral analysis to the current data and found that isoﬂurane had spinal effects that extended beyond its site of application. The reductions in spectral amplitude by isoﬂurane are consistent with previous studies, in which synaptic activity was completely blocked in the midportion of the spinal cord with a low-calcium, high-manganese solution. When
Isoflurane was selectively administered to the midportion of the spinal cord, the spectral amplitude of ventral root activity was dose-dependently reduced in all three compartments, with the greatest depression of activity occurring in the middle chamber, where isoflurane was present (figs. 4A and B). This demonstrates that isoflurane present in one region of the cord can interfere with motor output in other regions. In the lamprey, sensory neurons are not active during fictive locomotion, and motoneurons do not possess propriospinal projections. Therefore, the effects of isoflurane on spinal regions outlying its site of application seem to result from action on CPG interneurons with intersegmental projections.

A discrepancy between the current results and those of previous studies using synaptic blockade lies in the effects of each manipulation on cycle frequency in the rostral versus caudal compartments. A synaptic block in the previous studies decreased frequency in both the rostral and caudal compartments, whereas we observed that isoflurane only decreased cycle frequency in the caudal compartment (fig. 4C). Previous studies used different concentrations of D-glutamate to differentially activate the rostral and caudal regions of the spinal cord and found that caudal segments increase or decrease their cycle frequencies to more closely match those of rostral segments. Therefore, isoflurane could have decreased the caudal cycle frequency by decreasing the overall excitability of CPG networks in the middle compartment, which in turn resulted in slowing of the caudal rhythm. In contrast to blockade of all synapses, isoflurane and other volatile anesthetics have differential effects on multiple ion channels. This can result in complex effects on neuronal networks by both decreasing excitatory activity and enhancing inhibitory neuronal activity to depress motor output. From the current data, it is not possible to conclude how isoflurane affected different classes of excitatory and inhibitory neurons. However, long descending (caudal) projections in the lamprey spinal cord are primarily inhibitory. Therefore, isoflurane might decrease frequency in the caudal compartment by preferentially enhancing inhibitory activity. Because γ-aminobutyric acid–mediated activity slows the cycle frequency of fictive swimming in the lamprey, the decrease in cycle frequency could have resulted from potentiation of γ-aminobutyric acid–evoked currents in γ-aminobutyric acid type A receptors by isoflurane. Another explanation is that isoflurane depressed excitatory locomotor drive to the caudal segments to a greater extent than inhibitory drive, leading to a relative increase in descending inhibitory activity at higher isoflurane concentrations. In either case, the effect of isoflurane on frequency is likely attributed to its effect on asymmetrical CPG coupling rather than a gradient of preferred frequencies among spinal segments. This is supported by previous studies in which the rostral and caudal segments do not show differences in their intrinsic frequencies when they are surgically separated.

Isoflurane also decreased the coherence of activity between the rostral and middle chambers (fig. 5), indicating that the functional coupling that entrains the locomotor rhythm between these regions was disrupted. In the previous synaptic blocking studies, peak rostrocaudal coherence remained unaffected until approximately 16 spinal segments were blocked. Therefore,
coherence reduction by isoflurane was presumably attributed largely to its effect on neurons with relatively long axonal projections. Although many CPG neurons possess both rostral and caudal projections, they are anatomically and functionally asymmetrical, with caudal projections tending to be longer and possess greater synaptic strengths than equidistant rostral projections. \(^{22-24}\) Therefore, the neurons responsible for maintaining coherence might be those with medium to long descending projections.

**Application of the Lamprey Locomotor System to Anesthetic Action in Mammals**

Species differences and the use of reduced preparations must be taken into consideration when interpreting the current results in terms of anesthetic action on intact mammalian systems. Aside from the methodologic advantages to the lamprey isolated spinal cord preparation, its locomotor system shares several anatomical, functional, and pharmacologic properties with locomotor systems in mammals. Spinal locomotor systems are activated in both species by anatomically similar descending pathways, such as the locomotor-initiating pathway that descends from the mesencephalic locomotor regions into the spinal cord via synaptic relays in the ventromedial medulla. \(^{16,31}\) Both orders of species also possess spinal CPGs that can exhibit rhythmic right–left alternating oscillations that are coordinated across multiple spinal segments. \(^{49,52}\) In addition, both mammals and lamprey share the same neurotransmitter/receptor systems crucial for initiating and maintaining a normal locomotor rhythm, where glutamate and glycine receptors play key roles. \(^{53-55}\) Therefore, these important similarities seem to justify the use of the lamprey as a model for locomotor systems in higher-order vertebrates, at least from the spinal to brainstem level.

Several studies have used lamprey to study anesthetic effects on spinal locomotor systems and their descending inputs. \(^{20,56,57}\) As with mammals, the current study and others \(^{57}\) have shown that clinically relevant concentrations of anesthetics block motor output in the lamprey at the level of the spinal cord, further supporting the use of lamprey as a model for anesthetic immobilizing action. A previous study has shown that lamprey have aqueous halothane requirements (to prevent movement) of approximately 0.52 mm, \(^{20}\) slightly greater than that needed in mammals. \(^{1}\) The aqueous isoflurane concentrations used in the current study were also greater than those needed to prevent movement in mammals and likely reflect the increased isoflurane solubility at the relatively cold temperatures currently used. \(^{58}\) We are uncertain why there was not a linear relation between the gas-phase and the aqueous-phase concentrations across the entire concentration range used. Because the mean aqueous isoflurane concentration in the bath was 98.6 ± 1.6% SD of that in the Ringer’s bottle through which isoflurane vapor was bubbled, this was not likely due to isoflurane escaping the aCSF into the air above the bath. It is possible that we did not wait long enough for the anesthetic to equilibrate in the aqueous phase. In some of the cases, we first collected data at 1 or 1.5% isoflurane and then decreased the concentration to 0.5%. If we did indeed not wait long enough, this would tend to produce a falsely high aqueous isoflurane concentration at 0.5%. However, we still achieved concentration-dependent pharmacologic effects that included a near abolition of activity in the middle compartment at the highest isoflurane concentration and significantly decreased rostral–caudal coherence at the two higher concentrations (but not at the lowest). Moreover, this concentration range encompassed the minimum isoflurane concentrations needed to block movement in intact lampreys (using the same equilibration time).

A potential drawback to the current study is that we did not record ventral root activity elicited by a supramaximal noxious stimulus, as applied in a typical MAC determination. Although it is possible to elicit locomotor rhythms in the isolated spinal cord by noxious mechanical or electrical stimulation of an intact piece of tail, these responses are short-lived, irregular, and/or entail varying patterns of movement (i.e., withdrawal, struggling or turning). \(^{25,50,59}\) Because the hypotheses and method of data analysis in the current study required that the spinal cord exhibit stable fictive locomotion over relatively prolonged periods, these factors precluded us from using tail stimulation to elicit locomotion. Furthermore, because sensory input is not necessary for fictive locomotion, the current methodology allowed us to test isoflurane effects on motor output that is independent of any potential isoflurane action on sensory neurons. Nonetheless, our pilot studies indicate that isoflurane requirements to prevent noxious stimulus–evoked movement in intact lampreys are similar to those that currently disrupted or abolished fictive locomotion in vitro.

**Sites of Isoflurane Immobilizing Action in the Spinal Cord**

Several of our previous studies in rats and goats have shown that isoflurane has little to no effect on noxious stimulus–evoked responses of nociceptive dorsal horn neurons, \(^{11,60,61}\) and in some cases, responses were actually enhanced. \(^{11}\) These previous studies led us to propose that isoflurane blocks noxious stimulus–evoked movement by depression of more ventrally located classes of neurons, \(^{11}\) such as reflex/locomotor interneurons or motoneurons. In the lamprey, sensory neurons are not active during fictive locomotion, \(^{44}\) and motoneurons do not possess propriospinal projections. \(^{42,43}\) Therefore, the current data support our previous hypothesis and further suggest that the immobilizing effects of isoflurane are largely attributed to both a direct
segmental and indirect "extrasegmental" depression of interneurons comprising locomotor networks distributed throughout the spinal cord.

Further studies are necessary to identify the specific classes of interneurons on which anesthetics act to cause immobility. The relatively well-understood lamprey locomotor system and its established computational models may provide us with a useful template on which to build future hypotheses regarding anesthetic action from the receptor to the network level.

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