DIAGONAL LOCOMOTION IN DE-AFFERENTATED TOADS

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INTRODUCTION

A major question in neurophysiology has concerned the patterning of motor output —is sensory feedback from peripheral sense organs essential in establishing sequences of muscular contractions, or is sensory information only used to modify a set pattern which is generated by the central nervous system? Rhythmic and repetitive motor activities in several animals have been examined in attempts to answer this question (Sherrington, 1913; von Holst, 1939; Lissmann, 1946; Wilson, 1961; Ikeda & Wiersma, 1964; Roberts, 1969; Egger & Wyman, 1969). For studies of vertebrate locomotion, the classic preparation has been the ambulatory pattern of amphibians (Hering, 1893; Bickel, 1897). Gray (1939) and Gray & Lissmann (1940a, 1946a) performed a series of partial de-afferentations, and found that the more extensive de-afferentations produced greater loss of co-ordination and muscle tone. They reported that as long as one dorsal-ventral root pair was left intact the animals could maintain the basic diagonal walking sequence. However, when Gray & Lissmann examined 25 totally de-afferentated toads, they found that 'no sign of ambulatory co-ordination remained' (p. 122, Gray & Lissmann, 1946a). When they left a single dorsal root intact, but cut the motor root to that segment, they found that no amount of unpatterned sensory stimulation in the segment could induce the diagonal walking sequence. Thus, their results indicated that patterned sensory information, fedback from a segment which was rhythmically stimulated by ambulation, was essential to the production of the diagonal walking pattern.

Paul Weiss reported that one completely de-afferentated toad retained 'patterns of motor coordination . . . (which) maintain themselves in, qualitatively speaking—full integrity' (p. 469, Weiss, 1936a); however, he never supported his observation with additional examples. He also transplanted limbs in such a manner that the sensory feedback of a limb should be out of phase with that received by the limb in its normal position (1936b, 1941b); and found that this did not disturb the motor score for loco-motion. He concluded that properly timed sensory information was not necessary for diagonal locomotion.

Thus both Weiss and Gray did inconclusive de-afferentation studies from which they drew opposite conclusions. They both tried other approaches to strengthen their conclusions. Gray (1940b, 1946b) demonstrated the existence of reflexes appropriate for ambulation, but did not show that they are necessary for ambulation, Weiss (1936b, 1941a, b) performed developmental and limb transplantation experiments, but did not prove a central mechanism for the generation of the locomotor pattern.

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* Dedicated, in Memoriam, to Donald M. Wilson, our academic father and grandfather. He dared: in the secrets of nature, in the wildness of nature, and in man's nature.

In 1950 these two investigators published back-to-back papers in the *Symposia of the Society for Experimental Biology* claiming opposite results. Weiss stated that 'the well established fact that completely de-afferentated limbs continue to function without essential impairment of their co-ordination likewise proves that intramember co-ordination, cannot possibly be the result of chain reflexes' (p. 101, Weiss, 1950). Gray countered by saying that 'the evidence in support of a central ambulating rhythm in the toad must be regarded as inadequate' (p. 123, Gray, 1950) and again stated that 'we did not observe any sign of ambulatory co-ordination in animals in which the whole of the spinal nerves (II–XI) had been de-afferentated . . . At least one *intact* spinal nerve was an essential feature of all animals exhibiting ambulatory movements.' (p. 116, Gray, 1950). Since 1950 no new research has been performed on this question, although many textbooks (e.g. Bullock & Horridge, 1965; Hinde, 1970; Thorpe, 1963; Tinbergen, 1951) have discussed the issue.

We have performed a series of total spinal de-afferentations on the toad *Bufo marinus*, and find that after this total spinal de-afferentation the toads are still capable of generating the diagonal locomotor pattern. These results are a direct contradiction to those of Gray & Lissmann.

METHODS

Large *B. marinus*, obtained from the Lemberger Company, Oshkosh, Wisconsin, were kept at room temperature in aquaria with constantly running tap water and raised dry plastic platforms. Sulphadiazine in dialysis tubing, chalk and copper pennies were employed to control redleg. There was just one period when redleg appeared in our colony, but only healthy animals were used in the experiments. After surgery, animals were maintained individually in plastic boxes with daily water changes. The containers were sterilized with ultraviolet radiation before use, to reduce sources of infection.

Drugs

Anaesthetization was accomplished by partial immersion for at least $\frac{1}{2}$ h. in a solution of 2 % urethane or of 0·1 % MS-222 (ethyl *m*-aminobenzoate methanesulphonate, Eastman Organic Chemicals, no. 9671). In early experiments the animals were anaesthetized in the cold (6–12 °C) and were kept on ice during the operation in order to lower the metabolic rate, slow the heart beat, and reduce bleeding. Later the cold treatment was abandoned, as it appeared unnecessary and caused additional trauma for the animal. Animals treated with MS-222 bled very little and the muscles frequently appeared white as if the MS-222 had restricted somatic blood flow. Recovery of movement occurred within an hour after surgery, but these animals became somewhat lethargic 3–5 days after the operation. In contrast, animals anaesthetized with urethane were prone to considerably more (yet still minor) bleeding from small vessels of the skin, musculature and bone and required several days to regain activity. The advantage of urethane was the prolonged active life and good health of the animals after they recovered. Intra-muscular injections of Bicillin or topical applications of Bacitracin appeared to have little beneficial effect, as animals with no antibiotic treatments normally had clean wounds with little or no infection.

Surgery

A single incision was made dorso-medially extending from the base of the skull for a length of three spinal segments. The musculature was carefully severed from its attachments to the neural spine, neural arch, and transverse processes on the three vertebrae, causing very little damage to the muscles. A high-speed dental drill with compressed air drive was used to cut through the neural arch on either side of the spine allowing the ridge of vertebrae to be easily lifted off. This entry to the spinal cord caused little trauma to the nervous system, since no sharp pieces of bone were being pried away. There was very little pressure from the drill, which operates at about 1 oz. of pressure and stalls at 2 oz.

The dura mater was cut away and the blood vessels of the subdural space were carefully pushed to one side by gently stroking with a Q-tip. Frequently an incision through the vascular layer could be made without cutting any large blood vessels, but when a major vessel could not be avoided, it was cauterized to control bleeding. Finally, the thin transparent pia mater was slit and laid back. The appropriate dorsal roots were lifted individually on a small hook and severed between the cord and the dorsal root ganglion about 1–3 mm. from the point of emergence from the cord. The blood vessels which frequently lay adjacent to the roots were carefully avoided.

A small strip of Gelfilm was laid over the operated spinal cord and held in place by insertion of the ends into the spinal canal. The wound was sewed closed and the animal was allowed to recover.

Observations

The movement of the toads was recorded with a Bolex H 16 movie camera using tri-X reversal film. The animals were photographed at 12–16 frames/sec. from above and also from below as they moved along a glass plate. It was difficult to induce de-afferentated animals to move about while they were in the photographic chamber. Quick movements, moving shadows, and manipulations such as tilting the animal, appeared to be the most effective stimuli. Every toad was observed in locomotion at some time, but the movements were not always recorded by the camera.

A film analyser was used to view the developed film frame by frame in order to observe, describe and record each limb movement and its temporal relation to movements of the other limbs. The written description was then analysed to determine the sequence of protraction movements exhibited by the four limbs. Protraction is defined as the non-propulsive movement of a limb, which in amphibians is normally flexion; while retraction indicates a propulsive movement which is generally an extension. Attention was given to protraction rather than retraction for several reasons: historically ambulation has been described in terms of protraction sequence by Gray & Lissmann (1940*b*), Gray (1944), and others; protraction must be an active movement by the limb, in contrast to the passive retraction of a limb which may occur when the other limbs propel the body forward; and protraction normally has a shorter time course than retraction, which facilitates determination of a temporal sequence involving all the limbs. The locomotion of normal, control-operated and totally de-afferentated *B. marinus* was examined.

RESULTS

Normal locomotion

In normal adult *B. marinus* the usual mode of locomotion is jumping when on land and swimming when in water. Both of these forms of locomotion use the hind limbs in synchrony, rather than in alternation as during walking. The toads are seldom observed to progress by walking, and we were not able to induce them to walk. When placed on a solid surface, the animals squat on their hind legs with their forelegs supporting the body at an angle of 45°, and remain motionless for long periods of time. By prodding or sudden motions, we were able to induce only jumping. On the rare occasions when normal *B. marinus* were observed walking, the hind limbs raised the animal out of the squatting posture so that the hind quarters were almost as high as the forequarters.

The normal diagonal pattern of walking for tetrapods, including toads (Gray, 1944), is the protraction sequence: right-hind, right-fore, left-hind, left-fore, RH, RF, LH, LF, etc. This is the only sequence in which the animal's centre of gravity is always within a tripod of support while the fourth leg moves.

Operated animals

A series of 28 *B. marinus* was totally de-afferentated by severing all spinal dorsal roots. This normally meant cutting roots II–XI inclusive (root I is embryonic and is not present in the adult), but in one case an extra set of roots was cut which were similar, in size and in region of origin, to roots V, VI and VII. Histological examination did not reveal any other instance of unexpected additional roots. Another series of 12 toads served as operation controls. In these animals the spinal cord was exposed and the pia mater was cut, but some or all of the dorsal roots were left intact.

Extensive de-afferentation had quite severe postural effects. Muscle tone was generally weak or lacking, leading to an abnormal posture in which the body was not supported but lay prone on the ground. Some animals had somewhat better motor tone and supported their bodies slightly off the ground; these animals could be excited into movement which would be maintained for at least a short time. There was great variation in the degree of recovery after either sham operations or de-afferentating operations. Control animals in which up to four roots were left intact did not show less severe after-effects of the operation, or greater recovery of activity, than the totally de-afferentated animals.

Twenty of the totally de-afferentated animals were photographed; of these seven toads moved extensively during the cinematographic sessions, with each of the seven making over 100 protraction movements. Good filmed sequences of movement were obtained from four of the twelve control animals.

Every animal made locomotory movements of one kind or another. These included two different patterns of alternating leg movements as well as swimming and jumping movements. There were also many propulsive movements of the limbs which did not fit into any recognizable sequence. The list of limb protractions obtained from the films was analysed to see if the animals stepped in the 'normal' sequence with a more than random probability. We started by analysing pairs of steps.

The percentage of pairs which followed the 'normal' ambulatory pattern was calculated from the total filmed movements of the toads, e.g. calculating the number of times a protraction of RH was followed by protraction of RF as a percentage of the number of times RH was followed by protraction of any limb. Totally random movement would give a result near 25% since any one of the four limbs could be the next to protract following the recovery phase of any given leg, and all four possibilities were observed. A protraction followed by a jump or quiescent period was not included in the calculations. The best control animals and the best totally de-afferentated animals demonstrated almost identical readiness to move the appropriate hind limb following protraction of a foreleg, as shown in Table 1. In contrast, a hind-leg protraction was

Table 1. *Percentage of times a protraction of a forelimb was followed by a protraction of the hind limb which would be appropriate for the 'correct' ambulatory sequence*

Comparison of a totally de-afferentated toad (H) with a partially de-afferentated toad (R) and a sham-operated toad (C).

Toad	Number of dorsal roots cut	LF–RH	RF–LH
C	0	120/155 = 77%	120/155 = 77%
R	17	29/39 = 74	36/49 = 73
H	20	24/33 = 73	20/27 = 74

Table 2. *Percentage of times a protraction of a hind limb was followed by a protraction of the forelimb which would be appropriate for the 'correct' ambulatory sequence*

Comparison of the same toads as in Table 1.

Toad	Number of dorsal roots cut	LH–LF	RH–RF
C	0	91/142 = 64%	90/153 = 59%
R	17	29/43 = 67	31/40 = 77
H	20	20/65 = 31	12/45 = 27

followed much less often by the protraction of the appropriate forelimb, as shown in Table 2. Disuse of the forelimbs due to postural deficiencies appeared responsible for this lower value. In general, total or partial de-afferentation caused a lowering of the body posture with the forelimbs no longer supporting and elevating the anterior portions of the toad. This change in posture had little effect on the mechanics of hind leg movement, but greatly altered and hindered the freedom of movement of the forelimbs. The lowered posture not only changed the angle at which the forelimbs were able to move, but also a forelimb was frequently trapped under the body. In the summed records from the totally de-afferentated animals forelimb movements accounted for only 40% of the steps while hind-limb movements accounted for 60%. Thus, when a forelimb did move, it was normally followed by the appropriate hind limb; whereas a hind-limb movement frequently could not be followed by the appropriate, but trapped, forelimb, and the pattern was disrupted by protraction of the wrong forelimb or of the opposite hind limb. This latter caused frequent alternation of hind limbs, as high as 52–60% in toad H compared to 13–21% for a sham-operated toad.

The above data on pairs of steps include times when the toads were forced into

abnormal sequences owing to postural restrictions of a limb, e.g. a trapped forelimb. The pairs data also includes times when the toads seemed to be trying to swim or walk in either of two patterns (see below). The expected sequence of limb movements is different for each of these activities. However, a given pair of steps is a part of only one of the sequences. Hence from any pair of steps it can be predicted *uniquely* what the third step should be if the animal is indeed using a particular locomotory sequence. Similarly if any sequence of n steps fits one of the patterns, the $n+1$st step can be predicted. If the animal is moving its limbs randomly, these predictions should be borne out 25% of the time. In our totally de-afferentated animals the predictions are verified 66% of the time for sequences of four or more steps. The data is presented in Tables 3 and 4.

Table 3. *Percentage of times a given 'normal' sequence was followed by an additional correct step*

$n+C$ is the number of times n steps in the normal sequence is followed by another correct step; $n+A$ is the number of times n steps in the normal sequence is followed by any further step ($n = 2$, 3, 4, 5 and 6). Comparison of totally de-afferentated toads (K, AA, sum of all totally de-afferentated toads) with partially de-afferentated (R, 17 roots cut), and sham-operated (C).

Toad de-afferentation	K total	AA total	Sum of 20 total	R partial 17/20	C none
2+C/2+A	30/55 = 55%	26/46 = 56%	144/277 = 52%	31/38 = 82%	51/71 = 72%
3+C/3+A	21/28 = 75	18/23 = 78	79/119 = 66	19/26 = 73	45/49 = 92
4+C/4+A	12/18 = 67	15/17 = 88	42/63 = 67	13/14 = 93	25/37 = 67
5+C/5+A	8/12 = 67	9/13 = 69	24/39 = 62	10/11 = 91	22/23 = 96
6+C/6+A	6/7 = 86	6/8 = 75	17/21 = 81	4/6 = 67	14/17 = 82

Table 4. *Percentage of times a given 'reverse' sequence was followed by an additional correct 'reverse' step*

Toad de-afferentation	Sum of 17 total	C none
2R+C/2R+A	61/193 = 31%	19/44 = 43%
3R+C/3R+A	26/46 = 51	11/13 = 85
4R+C/4R+A	12/17 = 71	4/7 = 57
5R+C/5R+A	5/7 = 71	2/3 = 66

The normal forward pattern of RH, RF, LH, LF, etc., was observed fairly often; and once initiated, this pattern was usually maintained until the animal stopped walking. One totally de-afferentated animal made 12 sequential protraction steps following this normal pattern, but most of the toads ceased movements after fewer steps. The summed data from all the totally de-afferentated toads showed that when a toad made any protraction movement following three steps of the normal pattern, then the fourth step was the appropriate step for the sequence 66% of the time. When the preceding steps followed the normal pattern, the fifth step was correct 67% of the time; the sixth, 62%; the seventh, 81%; and the eighth, 41%. If there had been random movement, these percentages should have been near 25%. Table 3 shows the data for some individual toads which had been totally de-afferentated, partially de-afferentated, and sham-operated for purposes of comparison. Values are presented as ratios of the number of times the given sequence length was followed by a correct step to the number of times the given sequence was followed by any step. Notice that

similar results were obtained from toads which had received different amounts of de-afferentation.

We observed a second sequence of RF, RH, LF, LH displayed for brief periods by some of the operated toads. This sequence is the reverse of the normal sequence and propels the animal forward, but does not constantly provide a tripod of support. Reversed pairs of steps occurred almost as frequently (81 %) as normal pairs but longer sequences appeared less than half as often as normal sequences of corresponding length. The longest reversed sequence continued for ten steps. The tendency to display the reversed sequence varied greatly among the animals, but once the sequence was initiated it was maintained surprisingly well, in the sham-operated as well as in the de-afferentated toads, as seen in Table 4.

It should be emphasized that in Tables 3 and 4 the 'sum of 20' column and the 'sum of 17' column represent *all* the data from all the toads which moved while being photographed. There is no selection here for the 'better' animals.

The spinal cord of one totally de-afferentated toad was sectioned between the brain and the spinal cord, so the spinal cord had no sensory input at all. This animal, which remained alive for 12 days until it was killed, would occasionally move one leg. Pressure on the wound could induce single movements of one or both hind limbs, but the animal was extremely lethargic.

DISCUSSION

After complete spinal de-afferentation our animals still exhibited ambulatory patterns. Thus, the execution of an ambulatory behaviour pattern cannot depend on rhythmic excitation transmitted through the spinal sensory neurones.

Our results were not produced by regenerated neural connexions because many of our animals resumed ambulation the same day as the operation. Although regeneration within the central nervous system is supposed to be minimal, Butler & Ward (1965, 1967) found restoration of walking and swimming in *Ambystoma* and *Triturus* following ablation of the spinal cord, but restoration was delayed 40 days or more until some regeneration of the spinal cord was attained. Our experiments were carried out within a much shorter time scale; however, those of our animals which were allowed to live for several months after de-afferentation did not display noticeable differences in their behaviour as time progressed.

It is also unlikely that fatigue played a role in the patterning we observed. Since our statistical analysis of longer sequences starts only after two steps have been taken, it can be argued that these legs are fatigued and the remaining legs would have a higher probability of being moved next. We see no reason to think that one step of a leg should fatigue either the neurones or the muscles involved. It was not uncommonly seen that one leg alone would make repeated movements; and during periods of jumping, the legs would make several rapid movements in succession.

Our results are in contradiction to the observations made by Gray & Lissmann. Possibly the difference is related to our use of *B. marinus* in contrast to *B. bufo*. It is also possible that our surgery was less severe so that the animals were able to display the ambulatory movements which previously had been masked by poor recovery. Our surgical incision was less extensive as we removed only three neural arches in contrast to Gray's dissection of the entire vertebral column from the skull to the urostyle. Our

technique leaves a greater region of attachment of the postural muscles of the back. This may have been the significant difference, since even in our animals poor posture seemed to be the major impediment to locomotion.

Gray & Lissmann report no quantitative analysis of their data to support the conclusion that there was no sign of ambulatory co-ordination. Without quantitative analysis it is difficult to separate effects on the amount of motility from those on the *pattern* of locomotion. In our studies the amount of motility of the toads is greatly reduced, and it is only by quantitative analysis that it becomes unequivocal that the locomotory *pattern* is largely preserved.

It should be made clear that spinal de-afferentation does not settle the question of peripheral v. central patterning of locomotor activity. The cranial sense organs remain intact and, via the brain, are in communication with the spinal cord. Thus for instance, vestibular or optical information could be used as rhythmic cueing signals. It has never been determined whether cranial inputs are necessary, or sufficient, for locomotion. Gray & Lissmann (1947) performed bilateral labyrinthectomies in animals with spinal sensation intact and found that walking was still possible. Holmes (1927) reports that no portion of the brain anterior to the middle of the medulla is necessary for walking, as a brain section at mid-medullary level produces an animal which walks continuously. However, in spinal animals Gray & Lissmann (1940b) were unable to elicit walking. Our spinalized and de-afferentated animal showed no locomotor activity.

In normal toads the body is held off the ground so that on each step the anterior part of the animal is subject to lateral and rolling displacements. In our de-afferentated toads the posture was very much lower, often the whole body except the jaw was in contact with ground. This posture minimized, but did not eliminate, head motions with their consequent vestibular input. In further research the role of cranial input should be investigated directly. Perhaps the combination of a mid-medullary section to produce a continuously walking animal with elimination of all sensory input below the section will allow a final resolution of this problem.

SUMMARY

1. Twenty-eight toads (*B. marinus*) were de-afferentated by severing all spinal dorsal roots.

2. Every animal made locomotory movements of one kind or another. The normal diagonal pattern was observed fairly often; and, once initiated, this pattern was usually maintained until the animal stopped walking.

3. When a toad made any protraction movement following three steps of the normal pattern, then the fourth step was the appropriate step for the sequence in 66% of cases. When the preceding steps followed the normal pattern, the fifth step was correct in 67% of cases; the sixth in 62%; the seventh in 81% and the eighth in 41%. Random movement predicts 25% in all these cases.

4. It is concluded that spinal afferents are not necessary for the co-ordination of diagonal locomotion.

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