Discharge Patterns of the Slowly Adapting Mechanoreceptor Afferent Units Innervating the Non-warty Skin of the Frog

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Abstract Discharge patterns of slowly adapting (SA) mechanoreceptor afferent units innervating the non-warty skin of frogs, were analyzed statistically. Because SA units in the frog did not always produce sustained discharges for a long period, analysis was carried out on ensembles of interspike intervals (ISIs) obtained in two ways: (1) a series of successive ISIs obtained in the quasi-stationary state of maintained discharges and (2) an ensemble of ISIs ($X(1), X(2), \dots, X(50)$), obtained on repeated trials of stimulation at about 1,000 msec following the onset of stimulation. In some units these two types of ensembles of ISIs were collected. Statistical analysis of a series of successive ISIs in the quasi-stationary state disclosed two kinds of discharge patterns, irregular and regular, corresponding to those of the SA cutaneous units of mammals and reptiles. We named these two types of units Frog type I and Frog type II (Ft I and Ft II) units, respectively. In addition, the quantitative study of an ensemble of ISIs in the non-stationary state revealed that Ft II units discharged regularly in response to an optimum range of indentation but irregularly to indentation outside this range, although Ft I units produced irregular discharges irrespective of the magnitude of indentation applied.

Key Words: frog, slowly adapting mechanoreceptors, impulse patterns.

The presence of two different types of slowly adapting cutaneous mechanoreceptor afferent (SA) units has been reported in various animals, including mammals (CHAMBERS and IGGO, 1967; CHAMBERS *et al.*, 1972; HARRINGTON and MERZENICH, 1970; KNIBESTOL, 1975) and reptiles (KENTON *et al.*, 1971).

In our previous study (OGAWA and YAMASHITA, 1982) we found a single type of SA unit in the warty skin of the frog which produced irregular discharges in response to square wave indentation of the skin. Their receptive fields (RFs) were

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characterized by the presence of several sensitive spots in association with warts (OGAWA *et al.*, 1981; OGAWA and YAMASHITA, 1982). Thus, a close similarity between SA units of the warty skin of frogs and SA type I units of mammals was indicated. However, it is not known whether the SA units which innervate the non-warty skin of the frog are also only of the single type.

In the present study, we examined the discharge patterns of SA units innervating the non-warty skin of the frog toe, by collecting an ensemble of interspike intervals (ISIs), either during the quasi-stationary state of maintained discharges, or during the non-stationary state of discharges in response to several trials of standard indentations.

A preliminary report has been published elsewhere (OGAWA *et al.*, 1982).

METHODS

Preparation. American bullfrogs, *Rana catesbeiana*, of either sex, weighing ca. 300 g and having thick toes, were used. Experimental procedures were almost the same as used in previous experiments, and the details have been described elsewhere (OGAWA *et al.*, 1981).

Mechanical stimulation. As a standard stimulation, 250 μm indentation of 3 sec duration was applied 50 times to the skin through a moving coil transducer. To quantitatively study the discharge patterns of the SA units, two kinds of mechanical stimulation were further employed: (1) 50 trials of ramp and plateau indentations but of different magnitudes (*e.g.*, 150 and 400 μm), and (2) a large sustained indentation, *e.g.*, 250 or 500 μm , for more than 2 min by manually lowering a manipulator holding the moving coil transducer, to obtain a large number of maintained discharges.

Data processing. The procedures of data processing were almost the same as in previous experiments, and the details have been described elsewhere (OGAWA and YAMASHITA, 1982). For a small number of SA units, a maintained discharge was obtained in response to a large magnitude of indentation. After checking the stationarity (OGAWA *et al.*, 1974), an ensemble of successive ISIs in the quasi-stationary state was analyzed statistically, *i.e.*, by calculation of the mean interval and standard deviation (S.D.), and by ISI histogram. For most of the SA units, however, an ISI was measured for each of the 50 stimulations at 1,000 msec time points after the onset of stimulation. Fifty ISIs were then collected and pooled as an ensemble, *e.g.*, ($X(1)$, $X(2)$, $\dots$, $X(50)$) (NAKAHAMA *et al.*, 1977; OGAWA and YAMASHITA, 1982). The ensemble was then utilized for statistical analysis, after checking that no trend was present in it by using a *u*-statistic at a significance level of 5% (COX and LEWIS, 1966; NAKAHAMA *et al.*, 1977). In some units, two kinds of ensembles of ISIs were collected in order to compare their statistical properties.

The time-courses of the discharges were obtained on the post-stimulus time

(PST) histograms made over 50 trials, and analyzed in terms of time-constants by means of the standard "peeling off" procedure (PERL, 1960; GOTTSCHALDT *et al.*, 1973; OGAWA and YAMASHITA, 1982).

A microcomputer (MZ-80K, Sharp) was used to measure the ISIs with a time resolution of 1 msec and to construct a PST histogram. ISI histograms were tested for fit to Γ distributions with integer parameters. To test the goodness of fit to the Γ distribution, a χ^2 test (at the 5% level) was used (OGAWA and YAMASHITA, 1982).

RESULTS

All of the 31 SA units analyzed were selected from those innervating the plantar surface of the toe of the left hindfoot of the frog. They formed two groups as regards discharge patterns and adaptation behavior. One of the two groups ($n=9$) showed response characteristics similar to the slowly adapting type I cutaneous units of mammals (CHAMBERS and IGGO, 1967; CHAMBERS *et al.*, 1972; HARRINGTON and MERZENICH, 1970; KNIBESTOL, 1975) or of reptiles (KENTON *et al.*, 1971). Similarities in the response characteristics were observed for sustained as well as short repeated indentations of various magnitudes. But the other group ($n=22$) was similar in response characteristics to the slowly adapting type II cutaneous units of mammals (CHAMBERS and IGGO, 1967; CHAMBERS *et al.*, 1972; HARRINGTON and MERZENICH, 1970; KNIBESTOL, 1975) and reptiles (KENTON *et al.*, 1971), when an adequate indentation was applied. Therefore, we refer to them as Frog type I and Frog type II (Ft I and Ft II) units, respectively.

Discharge patterns produced in two different types of SA units for a sustained indentation

During a dynamic phase of skin indentation both types of SA units produced spikes of short intervals (dynamic phase of discharges), which was followed by gradual lengthening of interspike intervals (static phase of discharges) during sustained indentation of the skin (Fig. 1). The discharge patterns of Ft I units in response to a long lasting indentation showed a large variation in successive ISIs (Fig. 1A), in contrast to Ft II units with a small variation in the ISIs (Fig. 1B). Such a difference in discharge patterns between the two is well illustrated in the relation between the mean of the successive ISIs and their S.D. during the course of adaptation (Fig. 2). During the adaptation of Ft I response, the S.D. increased along with the mean ISI. In Ft II units, on the other hand, the S.D. remained small, except during the initial period of irregular bursts where the S.D. was very large. These characteristics of Ft I and Ft II units are comparable to those of sinus type I and sinus type II SA units of cats (GOTTSCHALDT *et al.*, 1973).

To quantitatively study the properties of discharge patterns of these two types of unit, an ensemble of the successive ISIs in the quasi-stationary state was collect-

Fig. 1. Impulse discharges of slowly adapting receptors in the non-warty skin of the frog in response to 500 μm indentation. A, Frog type I unit (20112); B, Frog type II units (71331). Logarithmic length of successive intervals (msec) are plotted on the ordinate. Horizontal bars indicate the period in which an ensemble of successive ISIs are in the quasi-stationary state.

ed and statistically analyzed. Ensembles of these ISIs of Ft I units had a large coefficient of variation (C.V.), ranging from 0.40 to 0.69 ($n=6$). The histograms of these ISIs gave a good fit to a Γ distribution of a small parameter, *e.g.*, 5 in Fig. 3A. The parameter of a best fit Γ distribution for ten Ft I units ranged from 2 to 6. No significant relation was found between a pair of successive ISIs in the quasi-stationary state, for they were scattered in the first quadrant, but grouped near the origin (Fig. 3C). These findings suggest that these units discharge spikes irregularly, showing no dependence on the length of an immediately preceding ISI, just as with the SA unit in warty skin (OGAWA and YAMASHITA, 1982).

Ft II units discharged more regularly as indicated by a small C.V. (ranging from 0.12 to 0.23; $n=13$) in the ensemble of ISIs in the quasi-stationary state and also by a good fit to a Γ distribution of larger parameters, *e.g.*, 43 in Fig. 3B. The parameters of a best fit Γ distribution ranged from 19 to 67. The joint interval histograms showed that pairs of successive ISIs were concentrated around the mean ISIs, indicating that they produce impulses regularly (Fig. 3D).

Discharge patterns of SA units in the non-stationary state

Two different discharge patterns in response to a prolonged displacement. All

Fig. 2. Successive variation in means and standard deviations calculated for ten consecutive interspike intervals in Frog type I (A) and Frog type II (B) units during sustained indentation. Same units as shown in Fig. 1. ● and ○ denote the mean and S.D., respectively.

Ft I units ($n=7$) and almost all of the Ft II units studied (14 out of 15) produced particular responses when tested with standard indentations ($250\ \mu\text{m}$, 3 sec). Two representative responses are shown in Fig. 4. The Ft I units produced an initial burst (dynamic phase) during the indentation and the initial part of the static phase of stimulation, the burst being followed by irregular discharges of gradually decreasing rate (static phase) (Fig. 4B). As seen in the SA units of warty skin, many Ft I units also showed "off" responses (OGAWA and YAMASHITA, 1982), but the latter were not unique to Ft I units. In almost all of the Ft II units (14 of 15), the initial burst was of short duration, confined at the indentation phase, and followed by regular static discharges. However, when closely observed, there existed a phase of irregular discharges between the initial burst and maintained discharges in some units (Fig. 4C), or a silent period in others. One Ft II unit produced discharge patterns rather similar to those of Ft I units, but it was observed only when tested with the standard indentation. On the other hand, this unit gave rise to regular discharges in response to a sustained displacement as well as to 50 trials of indentations of different magnitudes (see below).

In a majority (5 of 7) of Ft I and about a half (7 of 15) of Ft II units, the discharge frequency began to decline exponentially immediately after the displace-

Fig. 3. Interspike interval histograms (A, B) and joint interval histograms (C, D) of an ensemble of successive ISIs in the quasi-stationary state of discharge. A best fit Γ distribution for each of the ISI histograms is given in A and B. A and C, Frog type I unit (20112); B and D, Frog type II unit (71331).

ment reached its final value: when analyzed in the average PST histogram over 50 trials, two time constants, *i.e.*, τ_{d1} and τ_{d2} , were found in the time-course of adaptation (Fig. 5B). In the remaining two Ft I and eight Ft II units, a phase during which discharge rates increased (initial frequency-increasing phase) was also noticed before discharge rates began to decline (frequency-decreasing phase) (Fig. 5A); one time-constant (τ_1) was found in the former phase in all the units. On the other hand, two time-constants (τ_{d1} and τ_{d2}) were found in all two Ft I units and in five of the eight Ft II units in the latter phase, but in the remaining three Ft II units only one time-constant was observed, the value of which corresponds to τ_{d2} . In Ft I units, τ_1 was 0.07–0.08 sec ($n=2$), τ_{d1} 0.2–0.3 sec ($n=7$), and τ_{d2} 1.3–4.2 sec ($n=7$). In Ft II units, on the other hand, τ_1 was 0.02–0.17 sec ($n=8$), τ_{d1} 0.03–0.3 sec ($n=12$), and τ_{d2} 2.7–14.8 sec ($n=15$). Two time-constants in the frequency-decreasing phase of Ft I units were comparable to those of SA units in warty skin.

Fig. 4. Responses of slowly adapting units to repeated trials of standard square wave indentation (250 μm). A, output of a mechanoelectric transducer to monitor the movement of the probe of a mechanical stimulator. B and C, sample records from Frog type I (20112) and Frog type II (72311) units, respectively.

Statistical analyses were applied to an ensemble of ISIs of two groups of SA units, collected at around 1,000 msec after the onset of stimulation, *i.e.*, during the phase of maintained discharges (Fig. 6). C.V. was larger for Ft I units (0.41 to 0.66, $n=7$) than for Ft II units (0.14 to 0.28, $n=14$), with the exception of an Ft II unit having a large C.V. (0.43). The ISI histograms of Ft I units gave a good fit to a Γ distribution with small parameters (2 to 6, $n=7$), but almost all of the Ft II units showed ISI histograms which matched the Γ distribution of larger parameters (11 to 49, $n=14$). The one remaining Ft II unit had an ISI histogram fitted by a Γ distribution with a small parameter of 6. The joint interval histograms for ISIs at around 1,000 msec after the onset of stimulation revealed an absence of dependency between a pair of preceding and succeeding ISIs in Ft I units, while some dependency was present in Ft II units (Fig. 6C, D).

Dependence of discharge patterns on the indentation magnitude. Discharge patterns of five Ft I and six Ft II units were examined by applying two or three indentations of different magnitudes (Fig. 7). Ft I units produced irregular discharge patterns irrespective of magnitudes of indentation applied. With an increase in indentation magnitude from 150 to 400 μm , discharge frequency at the 1,000 msec period increased. Also, the parameter of the best fit Γ distribution increased, *e.g.*, from 2 to 9, but never exceeded the value of 10 which was true for most of the SA units innervating warty skin (OGAWA and YAMASHITA, 1982).

Fig. 5. Time-course of adaptation in Frog type I (20112) (A) and Frog type II (72311) (B) units. Solid circles represent average discharge rates (f) calculated over a period of 0.1 sec, plotted on a semilogarithmic axis. Straight lines were fitted by the method of least squares using the relation, $\log_e f = \log_e f_0 - t/\tau$, where f_0 is the initial frequency when the stimulus reached the plateau, t the time after stimulus reached the plateau and τ the time-constant of the exponential decline. To calculate the early time-constants, τ_{d1} and τ_1 , the early portion of the curve was replotted with open circles, and further with solid triangles (A), after subtracting the extrapolated line of the late portion of the curve. Values indicated by solid triangles were negative, but plotted in the same quadrant as if they were positive, for convenience. τ_1 , τ_{d1} , and τ_{d2} denote time-constants in the initial frequency-increasing phase, and early and late time-constants in the frequency-decreasing phase.

Two of the six Ft II units produced a highly regular discharge pattern, which was independent of the indentation magnitude, and the parameter of the best fit Γ distribution was always larger than 10. In the four remaining units, however, parameters of the best fit Γ distribution changed greatly depending upon the magnitude of indentation applied: one of the units showed an irregular discharge pattern at a small indentation magnitude (e.g., 200 μm), but produced a regular one at a larger indentation magnitude. The three other units produced a regular discharge pattern only at a lower range of magnitude of indentation, e.g., 150 μm , but an irregular pattern at a higher magnitude of indentation, e.g., 250 or 400 μm (see Fig. 7). The present findings showed that most of the Ft II units (4 out of 6) had an optimal range of magnitude of indentation to produce regular discharges. This is quite contrary to SA type II cutaneous mechanoreceptor units of mammals which produce regular discharges irrespective of the magnitude of indentation.

Fig. 6. ISI histograms (A, B) and joint interval histograms (C, D) of an ensemble of ISIs in the non-stationary state. For A and B, an ISI was measured at around the period including 1,000 msec after the onset of stimulation for each of 50 stimulation trials. Fifty ISIs were collected and pooled as an ensemble ($X(1), X(2), \dots, X(50)$) (ref. OGAWA and YAMASHITA, 1982). For C and D, ISIs at 1,000 msec time points (X_i) were plotted against the immediately antecedent ISIs (X_{i-1}), and the immediately succeeding ISIs (X_{i+1}) were also plotted against X_i . A and C, Frog type I unit (20112); B and D, Frog type II unit (72311).

General physiological properties

Neither of the two types of SA units in non-warty skin showed any background discharges. The indentation threshold of Ft I units ranged from 10 to 50 μm (mean = $19.4 \pm 11.9 \mu\text{m}$, $n=9$), being in the same range as that of Ft II units (mean = $25.7 \pm 10.1 \mu\text{m}$, ranging from 10 to 50 μm ; $n=22$). These values were significantly lower ($p < 0.05$, Student's t -test) than those for the SA units innervating warty skin (ranging from 10 to 150 μm ; mean = $44.3 \pm 28.8 \mu\text{m}$, $n=83$; Ogawa and Yamashita, unpublished observation). The critical slope of Ft I and Ft II units was less than 62.5 $\mu\text{m}/\text{sec}$, as seen in SA units in warty skin. All of the Ft I units ($n=9$) and most of the Ft II units (15 out of 22) had one or two spot-like RFs, and the area of one spot was as large as 0.5 mm^2 . Seven out of the nine Ft I units

Fig. 7. Dependence of discharge pattern upon indentation magnitude. While applying 50 stimulation trials with various magnitudes of indentation, an ensemble of ISIs at 1,000 msec after the onset of stimulation was obtained and the ISI histogram was constructed for each indentation magnitude. The parameter of the T distribution best fitted to the ISI histogram is plotted against the indentation magnitude. A, Frog type I units; B, Frog type II units.

had a single spot, and two had two spots. Also, 14 out of the 22 Ft II units had a single spot in the RF, and an RF containing two spots was found in only one unit. However, seven out of the 22 Ft II units had an elongated form of RF of an area ranging from 0.64 to 1.2 mm². The long axis of these RFs was situated in parallel to the longitudinal axis of the toe, except in one unit whose RF was located at the tip of the toe, with its long axis perpendicular to the longitudinal axis of the toe. The present finding is in contrast to that for SA units in the warty skin, these containing 4 to 17 spots in the RF (OGAWA and YAMASHITA, 1982). Both Ft I and Ft II units were excited by stretching the skin in any direction; none of them showed any preferred direction.

Conduction velocities of the SA units were measured by applying an electrical current to the nerve terminals through a pair of stimulating electrodes inserted into the skin of the RF. Conduction velocity of Ft I units was 14.3 ± 3.8 m/sec (ranging from 6.2 to 20.5 m/sec, $n=9$), and that of Ft II units, 14.6 ± 3.6 m/sec (ranging from 6.7 to 21.7 m/sec, $n=22$). There was no significant difference between these two values ($p>0.05$, Student's t -test). The latter were not very different ($p>0.05$, Student's t -test) from those of the SA units in warty skin (mean = 12.1 ± 2.2 msec; range 8.2–18.3 m/sec, $n=84$; Ogawa and Yamashita, unpublished observation).

DISCUSSION

Differentiation of two types of slowly adapting units in terms of discharge pat-

terns. In the present experiment, discharge patterns of SA units innervating the non-warty skin of the frog were studied by statistical analysis of an ensemble of ISIs. Two discharge patterns of SA units were distinguished in response to a sustained displacement of a large magnitude (*e.g.*, 500 μm), as seen in slowly adapting cutaneous mechanoreceptor afferent units of mammals (CHAMBERS and IGGO, 1967; CHAMBERS *et al.*, 1972; HARRINGTON and MERZENICH, 1970; KNIBESTOL, 1975) and reptiles (KENTON *et al.*, 1971). This finding was also confirmed by an analysis of an ensemble of ISIs collected during the non-stationary state of discharges. Accordingly, SA units were classified into two types. Frog type I units with irregular discharges and Frog type II units with regular discharges (Figs. 1 and 2). However, quantitative analysis of discharge patterns of the SA units in response to repeated stimulations of various magnitudes revealed that discharge patterns of some Ft II units changed depending upon indentation magnitudes; they produced regular discharges at an optimum range of magnitudes of indentation, but discharged irregularly outside this range. Discharge patterns did not depend upon the sites of stimulation in the RF of the same units if other parameters of stimulation were the same. The existence of this optimum range for regular discharges of SA units has not been described in other species. Ft I units, on the other hand, showed irregular discharges irrespective of the magnitude of indentation.

Different Ft II units had different widths of optimum range: in some of the Ft II units the optimum range to produce regular discharges was very narrow, but many other Ft II units produced regular discharges in response to indentations of various magnitudes (Fig. 7). The width of the optimum indentation range might be affected by the thickness of the soft tissue underlying the epithelium of the toe as well as by the thickness of the epithelium overlying the receptors. The threshold of cutaneous receptors is affected by the thickness of the corneal layer in the epidermis in cats (OGAWA and IGGO, 1977).

In the present paper, statistical analysis is described by an ensemble of ISIs collected at 1,000 msec after the onset of stimulation. An ensemble of ISIs collected at other time intervals after the onset of stimulation (*e.g.*, 500, 1,500, 2,000 msec) were also analyzed statistically: Ft I units produced irregular discharges throughout the whole static phase of stimulation. Ft II units gave rise to regular discharges, particularly at late time intervals (*e.g.*, 2,000 msec), but some of them produced irregular ones at the 500 msec time point, as seen in Fig. 4C. This phenomenon might be related to the passive process of recovery of the skin from the acute distortion brought about by skin indentation, as revealed in the time-course of the force applied to the skin after the onset of the steady indentation (PUBOLS, 1982).

General physiological characteristics and possible receptors concerned. SA units in warty skin and Frog type I units are similar to each other in that both produce discharges of a relatively high frequency at the onset of indentation, which

were followed by a rapid decline in the frequency of discharges. They then produce irregular discharges of a slowly adapting frequency which usually continue for 3–5 sec; however, some of the units discharge spikes as far as the indentation is maintained. SA units in the warty skin had sensitive spots associated with small elevations of the skin, *i.e.*, skin warts (OGAWA and YAMASHITA, 1982). All of the Ft I units in the non-warty skin had one or two sensitive spots in the RF. Those containing two sensitive spots in the RF were few (2 out of 7). A similarity in response properties between SA type I units of mammals and SA units in the warty skin of frogs was indicated in the previous study (OGAWA and YAMASHITA, 1982). The receptors of the SA type I units in the hairy skin of mammals were identified as Merkel cells (IGGO and MUIR, 1969). Since numerous Merkel cells were also found in the frog skin (FOX and WHITEAR, 1978; NAFSTAD and BAKER, 1973), and Ft I units behave like SA type I units of the mammalian skin, Merkel cells might be the receptors of Ft I units.

On the other hand, Ft II units give rise to a short burst of discharges, which, after various lengths of the period of irregular discharges or silence, are followed by a high level of maintained regular discharge. Although about two-thirds of the Ft II units (68.2%) had an RF of small size, the rest of the units had an elongated form of RF. The present finding suggests a similarity in the property of response between SA type II units of mammals and Ft II units of frogs. The receptor of SA type II units in mammals has been identified as a Ruffini ending (CHAMBERS *et al.*, 1972), but such a structure has not yet been found in the frog skin. In addition, Ft II units were different from SA type II units of mammals, for the former produced different discharge patterns depending upon the magnitude of indentation applied and did not show any preferred direction of stretching of the skin for excitation.

According to different response characteristics, CALOF *et al.* (1981) classified the SA units of the frog into two types, compression receptors and stroke receptors. However, the reported threshold stimulus forces of the latter (100–500 mg wt. and 300–4,000 mg wt.) were too large for comparisons to be made with the SA units in the present study. Also, the discharge patterns were not reported. Therefore, it is difficult to correlate them to the two types of SA units investigated in the present study.

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