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Nociceptors in the Gills of the Dogfish *Squalus acanthias*

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Summary. 1. One hundred and twenty two receptor afferents which discharged in response to an intra-arterial injection of 20 μg of phenyl diguanide were dissected from 72 isolated perfused gills of the spiny dogfish, *Squalus acanthias*: the mean spontaneous discharge rate at 13 °C was 0.4 ± 0.5 impulses $\cdot s^{-1}$. The maximum discharge rate in response to an injection of PDG was 10.5 ± 7.5 imps. $\cdot s^{-1}$: the discharge persisted for 56.8 ± 44.3 s. Discharge also occurred in response to an injection of 20 μg of 5 hydroxytryptamine.

2. Many of the receptors could also be discharged by 1 mm^2 pieces of dry filter paper previously soaked in PDG, placed on the external surface of the gill filaments.

3. The receptors were sensitive to light mechanical stimulation of the gill filaments; some parts of receptive fields which respond to mechanical stimulation failed to discharge in response to externally applied PDG.

4. Receptive fields varied in extent; some occupied less than one filament and others extended over several filaments.

5. Intra-arterial injections of 10 mg alloxan caused a rise in perfusion pressure and the development of a patchy oedema. At varying intervals following the rise of pressure the receptors commenced a prolonged slow discharge; many but not all also showed a brief short-latency discharge in response to the chemical stimulus of alloxan.

6. The many resemblances of these gill receptors to the type J and lung irritant receptors of mammals are discussed: it is suggested that they are unspecialised nociceptors of the gills and resemble the kind of structures from which the more differentiated mammalian respiratory nociceptors of alveolus and airway have been derived.

Introduction

The now classical studies of Paintal (1955, 1957, 1969) of pulmonary afferent fibres in the vagus nerve of the cat led to the recognition of receptors believed to lie in the interstitial tissue between pulmonary capillaries and the alveolar wall. These juxtapulmonary capillary receptors (= type J receptors) were found to discharge in response to various agents which had in common that they increased interstitial fluid volume and pressure and thus caused pulmonary oedema. Examples were, increase in pulmonary vascular pressure, microemboli, chlorine gas, and the drug, alloxan. In cats, type J receptors are specifically stimulated by the synthetic amidine drug phenyl diguanide, PDG. It had previously been shown that when PDG was injected into the lung circulation it reflexly evoked apnoea and shallow breathing, bradycardia and hypotension (Dawes and Fastier, 1950; Dawes and Mott, 1950; Dawes et al., 1951). Later studies revealed a somatic reflex response; intra-right atrial PDG caused an inhibition of the monosynaptic and other spinal reflexes (Deshpande and Devanandan, 1970; Ginzel et al., 1971; Kalia, 1973). Paintal (1970) suggested that this response, termed the J reflex, is a protective reflex that guards the lung against the danger that excessive activity of venous muscle pumps in exercise might overload the pulmonary circulation. The rise in pulmonary capillary pressure, and increased hydration of interstitial tissue, discharged type J receptors: this inhibited muscle activity and reduced the return to the right heart. On this view, type J receptors are primarily concerned in sensing

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Abbreviations: PDG, phenyl diguanide; *type T receptors,* juxtapulmonary capillary receptors

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the onset of oedema. Widdicombe (1974) suggests that they may have additional functions and that they should be regarded as a type of pulmonary nociceptor specialised for their location in the alveoli.

Whilst much of our understanding of the function of type J receptors derives from studies on the cat, other work suggests they are present in the rabbit (Guz and Trenchard, 1971), dog (Coleridge et al., 1965) and man (Jain et al., 1972). More recently Satchell (1978) reported that when 200 μg kg^{-1} of PDG was injected into the ductus cuvieri of the dogfish *Squalus acanthias*, it evoked apnoea, shallow-breathing, bradycardia, hypotension, and a brief cessation of swimming. These responses are similar to those of the mammalan J reflex. Moreover electrical stimulation of the central end of a cut branchial nerve caused similar responses suggesting that they are reflex in origin and arise from branchial receptors discharged by PDG. This paper reports the results of a study of afferent fibres which discharge in response to an intraarterial injection of PDG, in isolated perfused gills of dogfish.

Methods and Experimental Procedure

Specimens of *Squalus acanthias* 0.8–4.5 kg wt were trawled off the Otago coast and retained for a few days in holding tanks at the Marine Station. They were heparinised, 2500–5000 I.U. 30 min prior to dissection and pithed posteriorly and anteriorly. An afferent branchial artery running to one or other of the four branchial arches was cannulated and attached to a 50 ml syringe filled with oxygenated elasmobranch saline (Capra and Satchell, 1977). The gill was flushed with saline at intervals during the dissection. The afferent and efferent arteries were dissected free and the branchial nerve cleared back to its junction with the vagus ganglion at the rostral end of the anterior cardinal sinus. The entire branchial arch with its attached hemibranchs, afferent and efferent arteries and nerve was then transferred to a perspex cell.

This consisted of two compartments separated by a partition. The gill rested on a perforated shelf in the larger compartment above a layer of sea water and was washed with sea water from time to time. The perfusion cannula entered this compartment. The branchial nerve passed through a slot in the partition into the smaller compartment in which it was dissected. The whole cell rested on the stage of a binocular microscope. The gill was perfused with elasmobranch saline delivered by a roller pump at rates of 0.66–3 ml min^{-1}; drugs could be injected into a rubber cuff at the junction of the perfusion line with the cannula. The perfusion pressure was monitored by a pressure transducer and recorded on a polygraph. Two μg of isoprenalin were routinely injected into the afferent branchial artery at the start of the perfusion, to counteract the initial vasoconstriction which often followed the removal of the gill.

The small compartment contained a black perspex plate on which the nerve was dissected. Following removal of the sheath and subdivision, successive strands were laid across the recording electrodes. Discharges were recorded on tape and displayed on an oscilloscope and audiomonitor. Strands were examined for their content of fibers which would discharge in response to an injection into the perfusion line of 20 μg of PDG. Higher doses only slightly increased the rate and duration of discharge but caused greater tachyphylaxis; 15 min was allowed to elapse between each injection. Unitary discharges were obtained by successive subdivision of the strands. The cell for nerve dissection was kept moist with elasmobranch saline. Both compartments could be covered with close-fitting lids; preparations continued to yield active fibres for periods of 4–5 h. All investigations were carried out in a constant-temperature shielded room maintained at 13 °C ± 1 °C. Discharge rate is presented as the mean ± S.E.M.

Results

The Occurrence of PDG Sensitive Receptors in the Gills

Squalus acanthias has 9 hemibranchs on each side of the pharynx; 8 of these, the second to the ninth of the series, occur as four pairs on the rostral and caudal faces of the first four branchial arches. These four arches yielded the following numbers of successful preparations of isolated gills; the first 20, the second 23, the third 18 and the fourth 11. From this total of 72 isolated gills, 122 receptor afferents were isolated. The first hemibranch of the series of nine lies on the caudal face of the hyomandibular arch; its massive skeleton makes it unsuitable as an isolated preparation, and it was examined only in some preliminary preparations. Nevertheless, these showed that receptors were present which were discharged by PDG. Receptor afferents were isolated with almost equal facility from the pretrematic branch of each branchial nerve which receives fibres from the caudal hemibranch of the gill and from the sensory division of the posttrematic branch from the rostral hemibranch. Together these findings show that these receptors occur in all nine hemibranchs.

The Spontaneous Discharge Rate and the Response to PDG and to 5-Hydroxytryptamine

When first isolated the fibres were found to be either silent or discharging very slowly. The mean spontaneous discharge rate of 103 fibres during the period (10–70 s) prior to injection was 0.4 ± 0.5 impulses s^{-1}, with a range of 0–2.5; 42% discharged at rates below 0.1 imp. $\cdot s^{-1}$.

The maximum discharge rate in response to an injection of PDG was 10.5 ± 7.5 imp. $\cdot s^{-1}$ with a range of 0.7–36; 54% were in the range of 0.7–8.0. Following an injection of PDG the final return of the discharge to the resting level was sometimes prolonged; it was recorded in full in 28 fibres; their discharge persisted for 56.8 ± 44.3 s. Those that discharged at higher rates took longer to return to the resting level.

One such unit with a maximum rate of 28 imp.·s^{-1} discharged for 238 s. A further 7 fibres had discharges lasting for 100–160 s. Doubling the amount of PDG did not noticeably increase the maximum rate of discharge.

The response to injected PDG showed the phenomenon of tachyphylaxis very strongly. The discharge caused by the initial injection was always much greater than that to a second shortly thereafter. It was found necessary to leave an interval of 15 min for full sensitivity to return.

PDG is known to stimulate receptor sites responsive to 5HT; 24 fibres which had previously discharged in response to PDG were tested with injections of 20 μg 5HT. All were stimulated by this drug. There was a close correspondence in the maximum rate and duration of the discharges elicited by the two agents. 5HT was able to initiate discharge when applied to the external surface of the gill. The stimulant actions of 5HT were not blocked by methysergide when injected as a bolus injection in amounts 100 X that of 5HT. Methysergide is known to block the motor actions of 5HT on smooth muscle.

The Response to PDG Applied to the External Surface of the Gill

An observation that these receptors could sometimes be discharged by a solution of PDG dropped on the external surface of the gill led to a refinement of this method. A 10 mm × 50 mm strip of filter paper which had previously soaked up 500 μg of PDG in solution was air dried and cut into 1 mm^2 pieces; each square thus contained approximately 1 μg of crystalline PDG and could be placed precisely on the receptive field. The pieces were washed off with a jet of sea water: 14 receptive fields were explored by this method. It was noticeable that no tachyphylaxis occurred with this method of stimulation, presumably because a different region of a receptor dendrite was discharged with each application.

The discharge latency to PDG applied in filter paper islands varied greatly in different parts of each receptive field. An example is shown in Fig. 1; sites 2 and 4 had latencies of 17 s and less than 2 s respectively. In another receptive field (Fig. 2A) which extends across 16 filaments, latencies varied from more than 7 s to a few tens of ms. These short-latency discharges occurred as soon as the filter paper touched the surface. In some the stimulus led to a fluctuating rhythmical discharge (Fig. 1.4). Armstrong et al. (1976) report that starch emboli cause similar sporadic bursts of discharge from type J receptors in cats. The varied discharge latencies observed in different parts of a receptive field presumably reflect the fact that receptor dendrites lie at different levels within or beneath the epithelium of the filament and that it may take some seconds for the PDG to achieve a stimulant concentration there.

These receptors appear to have inherent differences in their excitability to PDG whether it is injected intra-arterially or applied to the gill surface. There is a significant correlation ($r=0.8$, $P<0.01$) between the maximum rate of discharge of 13 receptors stimulated by these two routes.

The Response to Mechanical Stimulation

The receptors could be discharged by gently stroking the external surface of the gill filaments. A very fine wire mounted in a glass rod was moved lightly along the length of each filament in turn (Fig. 1A–F). It is difficult to be sure how localised such a stimulus is; traction may be imparted to structures remote from the tip of the stimulator. Nevertheless it appeared that the surfaces of the filaments are very sensitive and the secondary lamellae are much less so. It may be that the rather few discharges observed when the tips of the secondary lamellae were stroked, derived from endings in the bases adjacent to the core tissue.

Figure 1 compares the response of a receptor to mechanical stimulation with that caused by externally-applied PDG. Mechanical stimulation commonly gave rise to a greater rate of discharge than PDG. Discharge occurred only as the tip of the stimulator traversed the filament; the receptors appear to be rapidly adapting like the irritant receptors described by Sampson and Vidruk (1975) in the canine lung. Even the small stimulus of placing the filter paper islands onto the receptive area elicited two or three action potentials (Fig. 1, 1–6). Some parts of receptive fields which responded to mechanical stimulation did not discharge in response to external PDG. This is seen in Fig. 1 at site 1 towards the end of filament D.

The Shape and Extent of Receptive Fields

The receptive fields of 15 units were mapped in detail by mechanical stimulation; six are shown in Fig. 2. The extremes are represented by A which extends over 16 filaments and C which occupies part of one filament. Interest attaches to E in which groups of three and of two responsive filaments are separated by three filaments from which discharges could not be elicited. These fields are certainly larger than the 1–3 mm

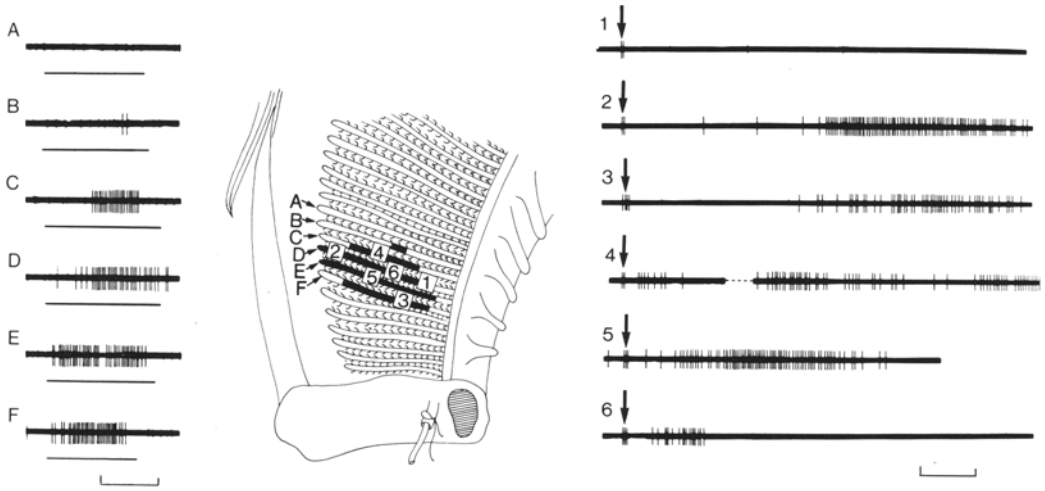

Fig. 1. Discharge patterns of a branchial receptor. The receptive field is marked in black. Oscilloscope traces A–F (left) record discharge caused by lightly stroking filaments A–F; black line records duration of the stimulus. Traces 1–6 (right) record discharge evoked by PDG soaked filter paper islands 1–6. Arrow marks moment of application: 5 s have been removed from the break in trace 4 to show the recurring bursts of discharge. The brief response to the mechanical stimulus of the filter paper is well shown in traces 1–6. The filter paper islands have been enlarged $\times 2$ in the illustration. Spikes retouched. Time calibration 5 s

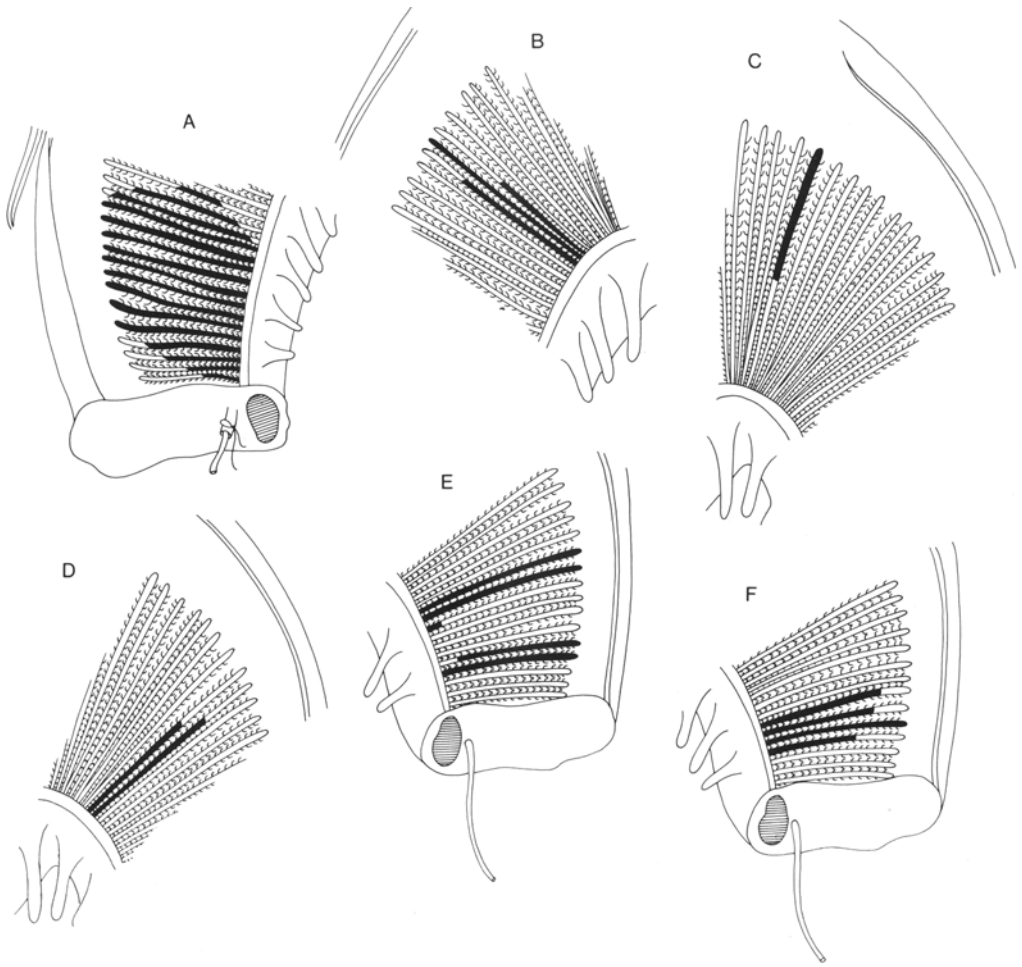

Fig. 2. Six receptive fields located in different regions of a gill: in E the field is broken into two parts separated by 3 unresponsive filaments

square of the intrapulmonary airway C fibre endings of dogs, reported by Coleridge and Coleridge (1977). When account is taken of other units less completely investigated than these 15, it becomes clear that there are no filaments not represented in one receptive field or another.

The Response to Alloxan

In the cat (Peralta, 1945), and dog (Staub et al., 1967) intravenous alloxan causes pulmonary oedema. There is an initial rise in pulmonary vascular pressure and this was at first thought to be responsible for the outflow of exudate into the alveoli. Later work attributed the oedema to an increased permeability of the alveolocapillary barrier as it occurred also in isolated perfused lungs (Goetzman and Visscher, 1969). In the cat type J receptors discharge at rates of 7.5 ± 6.3 impulses $\cdot s^{-1}$ for a sustained period following the onset of oedema (Paintal, 1969).

Eighteen isolated gill preparations all showed a rise in perfusion pressure following the injection of 10 mg of alloxan. As dogfish have ten gills this dose is equivalent to 25–100 mg $\cdot kg^{-1}$; this is less than the dose, 150 mg $\cdot kg^{-1}$ used in mammals. Pressure began to rise within 2 min and reached a peak of 18–128% of the basal perfusion pressure in 5–15 min. A patchy oedema developed in which the swollen tips of the secondary lamellae protruded from the spaces between the gill filaments. The pressure returned to normal in 40–146 min.

The discharge of 44 units was followed. All but three of these showed an initial early discharge at the same latency as that caused by PDG, and attributable to the chemical stimulatory effect of alloxan. This was followed by a second phase of discharge as oedema developed. Type J receptors lack this initial discharge. The unit portrayed in Fig. 3 is typical of the three that showed only the later discharge. This commenced 1 min following the peak of pressure and attained its maximum rate 9 min after. In 13 of the 41 units the direct chemically-mediated discharge returned almost to the baseline (Fig. 4) before the second phase commenced, 20 s to 6 min after the peak of pressure. In other units the separation between the two phases was less clear. In some the oedema developed rapidly and the initial chemically-mediated discharge had only begun to decline when it was overtaken by and merged with the prolonged second phase. The rate of discharge during the second phase was related to the inherent rate of the receptor. Some achieved peak discharges of 4–5 imp. $\cdot s^{-1}$; other, slower-firing units accelerated to a peak of 0.5–1 imp. $\cdot s^{-1}$.

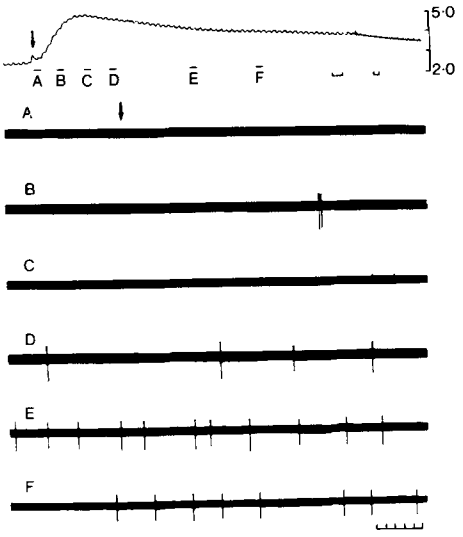

Fig. 3. Change in perfusion pressure and in discharge of a receptor in response to injection of 10 mg of alloxan at arrow. Upper trace is a polygraph record of perfusion pressure with constant volume delivery; pressure calibrations in kPa, time calibrations = 1 min. Traces A–F are oscilloscope recordings of receptor discharge during periods A–F on upper trace. Oscilloscope time calibration = 5 s. The peak of discharge, E, occurs 9 min after the peak of pressure

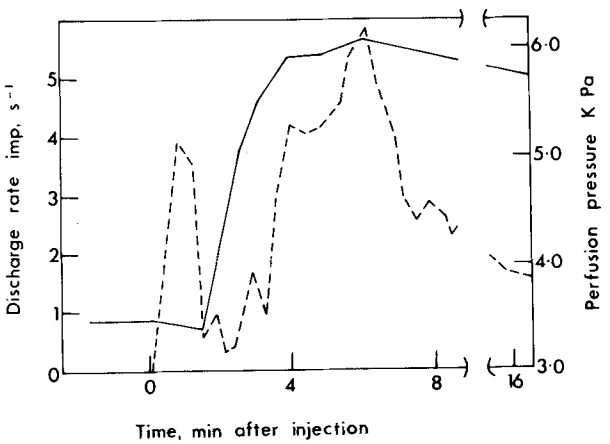

Fig. 4. A graph showing, solid line, the change in perfusion pressure following injection of 10 mg alloxan, and, broken line, discharge rate of a branchial receptor. In contrast to Fig. 3 this receptor shows a brief short-latency discharge caused by the chemical stimulus of alloxan: after a delay, the prolonged second phase of discharge, related to development of oedema, sets in. Each point on the graph is average discharge over the preceding min

Discussion

The responses of these branchial receptors resemble those of certain receptors located in the alveoli and airways of mammals. Branchial receptors are discharged by PDG; this drug also discharges the type J receptors of cats (Paintal, 1955; Armstrong and Luck, 1974), the intrapulmonary C fibre endings in

the airways of dogs (Coleridge and Coleridge, 1977) and lung irritant receptors from the intrapulmonary airways of rabbits (Mills et al., 1969). Both branchial and type J receptors of cats are discharged by 5HT (Paintal, 1957). The branchial receptors are sensitive to mechanical stimuli as also are type J receptors, intrapulmonary airway C fibre endings and lung irritant receptors.

In fish as in mammals the receptors must be located close to both vascular and respiratory surfaces for they can be discharged by agents delivered through the blood stream or in the respiratory medium. In cats (Paintal, 1969) type J receptors are discharged by the insufflation of halothane into the trachea. 1 μg of dry PDG or 5HT applied to the external surface of the gill will discharge the receptors beneath.

There are similarities in discharge rate. The spontaneous discharge rate of the branchial receptors, 0.4 ± 0.5 imp.$\cdot s^{-1}$ is similar to that, 0.3 imp.$\cdot s^{-1}$ reported by Armstrong and Luck (1974) for type J receptors in the cat. The maximum rates attained in response to PDG injection, 10.5 ± 7.5 imp.$\cdot s^{-1}$ are not greatly different. The discharge rate of lung irritant receptors in the rabbit is 11.3 ± 4.7 (Mills et al., 1969); that of type J receptors in the cat is 19 ± 7.9 (Paintal, 1969).

Finally there is the similarity that these receptors exhibit a prolonged discharge in response to oedema. Paintal (1969) has investigated the response to the oedema caused by the drug alloxan. In the gill as in the lung this causes a rise in perfusion pressure. The interval, of up to 9 min, which elapses between the peak of pressure and the peak of discharge is, Paintal (1969) suggests, the time it takes for the fluid to accumulate in the interstitial tissue. The majority of the gill receptors proved to be sensitive to the chemical stimulus of alloxan but even this distinction between them and type J receptors may prove a relative one for one of the 8 receptors described by Paintal (1969) showed a brief short latency discharge. Sellick and Widdicombe (1969) report that mild pulmonary congestion of the rabbit lung caused by inflating a balloon in the left atrium increases the discharge of lung irritant receptors. Certain of the C fibre receptors in the dog lung show a similar response (Coleridge and Coleridge, 1975).

The structure and location of these receptors is currently under investigation. Our preliminary studies and the published account of Kempton (1969) agree in showing a fine strand of fibres running the length of each filament to join the branchial nerve in the gill bar. The receptive fields (Fig. 2) suggest that parallel receptor dendrites must pass centrally along adjacent filaments. How the dendrites are arranged so that a receptor can respond to externally applied and injected PDG or 5HT is unknown. As the receptors must be much branched structures anyway, it may be that separate dendrites extend internally into the vascular spaces beneath the secondary lamellae.

The role of these receptors in the dogfish remains conjectural. We have noted that when PDG is injected into the branchial circulation of an intact fish it causes bradycardia and hypotension and an inhibition of breathing and locomotion. As PDG also discharges these branchial receptors it is reasonable to suppose that the reflex responses originate from them. Their position on the gill filaments is well suited to a role as branchial nociceptors, for any harmful mechanical or chemical influence carried in the incoming water must impinge on the filament surface prior to passing into the spaces between the secondary lamellae. Inhibition of ventilation and of forward movement are both appropriate protective responses to diminish the ingress of water. The receptors also respond to oedema. Bradycardia, peripheral vasodilation, and a reduction of the activity of muscle-operated venous pumps are all likely to reduce vascular pressures within the gills. We are uncertain whether raised blood pressure within the gills causes branchial oedema; if the balance of vascular pressure and colloid osmotic pressure operates as it does in the lung (Satchell, 1978) then these responses will protect the gill against this hazard.

The nomenclature of pulmonary receptors is in a period of change (Widdicombe, 1977; Coleridge and Coleridge, 1977). Alveolar type J receptors may be inappropriately named as they may extend into the atria, alveolar ducts and respiratory branchioles (Armstrong and Luck, 1974). Lung irritant receptors show resemblances to similar structures outside the lung, within the larynx (Boushey et al., 1974). Widdicombe (1974) suggests that both type J and lung irritant receptors should be regarded as belonging to a more generalised class of respiratory nociceptors. It is of interest that the branchial receptors described in this paper share so many features in common with them. From some such generalised respiratory nociceptors of lower vertebrates the mammalian respiratory nociceptors, specialised in relation to their location in alveolus or airways, may have differentiated.

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