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Influence of dendritic morphology on axonal competition

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Abstract

The development of nerve connections involves competition among axons for survival promoting factors, or neurotrophins, which are released by the axons' target cells. We have extended our model of axonal competition (van Ooyen and Willshaw, Proc. R. Soc. B. 266 (1999) 883–892) to study the influence of the target's dendritic tree on competition. We show that spatial separation of innervating axons on the target's dendrites mitigates competition and permits the coexistence of axons. The model accounts for the finding that in many types of neurons a positive correlation exists between the size of the dendritic tree and the number of innervating axons surviving into adulthood (Hume and Purves, Nature 293 (1981) 469–471; Purves and Hume, J. Neurosci. 1 (1981) 441–452). Our results emphasize the importance of postsynaptic dendritic morphology in the development of specific patterns of nerve connections.

Keywords: Competition; Neurotrophins; Dendrites; Morphology

1. Introduction

The development of connections between neurons and their target cells often involves an initial stage of hyperinnervation followed by elimination of axons [7]. Competition among innervating axons for target-derived neurotrophins, which are taken up by the axons via specific receptors at their terminals [1] and which affect the

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growth and branching of the axons, is thought to be involved in the elimination of axons [9].

In many types of neurons, a positive correlation exists between the complexity of the dendritic tree and the number of innervating axons surviving into adulthood [6,8]. In the ciliary ganglion of adult rabbits, for example, neurons that lack dendrites are innervated by a single axon, whereas neurons with many dendrites are innervated by the largest number of axons. This is not a matter of available space, since in newborn animals all neurons are innervated by approximately the same number of axons. The presence of dendrites somehow mitigates the competitive interactions involved in the elimination of axons.

In this paper, we offer an explanation for this phenomenon, using a compartmental version of our model of axonal competition [11]. Before introducing the compartmental version, we summarize [11] in the next section.

2. Competition for neurotrophins

In [11], a single target cell (e.g. a neuron) is considered at which there are n innervating axons each from a different neuron (Fig. 1). Neurotrophin is released by the target into the extracellular space (which is considered to be a single compartment) at rate σ and is removed by diffusion and degradation with rate constant δ. In addition, at each axon i, neurotrophin is bound to receptor, with association and dissociation constants $k_{a,i}$ and $k_{d,i}$, respectively. Bound neurotrophin (neurotrophin-receptor complex) is then internalized and degraded with rate constant ρ_i. Finally, unoccupied receptor is inserted into each axon at rate ϕ_i and is degraded with rate constant γ_i. Assuming standard reaction dynamics, the rates of change of the total amount of neurotrophin-receptor complex on axon i (C_i), the total amount of unoccupied receptor

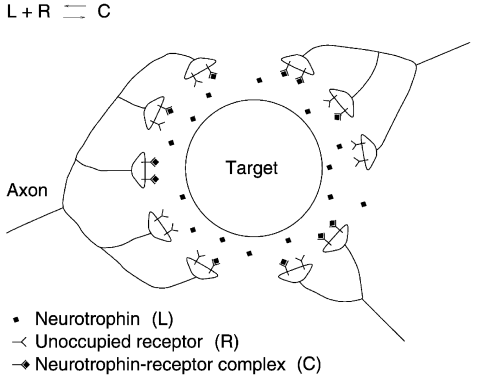

Fig. 1. Target cell with three innervating axons. The target releases neurotrophin, which is bound by neurotrophin receptors at the axon terminals. From [11].

on axon i (R_i), and the extracellular concentration of neurotrophin (L) are

$$\frac{dC_i}{dt} = (k_{a,i}LR_i - k_{d,i}C_i) - \rho_i C_i, \tag{1}$$

$$\frac{dR_i}{dt} = \phi_i - \gamma_i R_i - (k_{a,i}LR_i - k_{d,i}C_i), \tag{2}$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n} (k_{a,i}LR_i - k_{d,i}C_i)/v, \tag{3}$$

where v is the volume of the extracellular space, which is assumed to be uniform with respect to the concentration of neurotrophin.

Neurotrophins, following binding to receptor, enhance axonal growth: they increase the arborization of axons (and hence the number of axon terminals, where the neurotrophin receptors are located) [10,3], enlarge the size of the axon terminals [4], and possibly upregulate the density of neurotrophin receptors [5]. In all these effects of neurotrophins on axonal growth, the axon's total amount of receptor will increase. Therefore, the amount of unoccupied receptor that is inserted into the axon per unit time, ϕ_i, must be an increasing function, $f_i(C_i)$ (called growth function), of the amount of bound neurotrophin, C_i. One of the functions studied in [11] is $f_i(C_i) = \alpha_i C_i$. To take into account that axonal growth is relatively slow, ϕ_i lags behind $f_i(C_i)$ with a lag given by

$$\tau \frac{d\phi_i}{dt} = f_i(C_i) - \phi_i, \tag{4}$$

where the time constant τ for growth is of the order of days.

The precise values of the parameters of growth (α_i) and neurotrophic signalling ($k_{a,i}$, $k_{d,i}$, ρ_i, and γ_i) will vary among axons. For example, increased presynaptic electrical activity increases the axon's amount of neurotrophin receptor [2], which implies that increased presynaptic electrical activity affects growth (i.e. higher α_i) or neurotrophic signalling (e.g. a lower γ_i) or both.

Axons that at the end of the competitive process have no neurotrophin ($C_i = 0$, equivalent to $\phi_i = 0$) are assumed to have withdrawn or died. For $f_i(C_i) = \alpha_i C_i$, elimination of axons takes place until one axon remains, regardless of the supply of neurotrophin, σ (if $f_i(C_i)$ is a saturating function, several axons may survive [11]). The axon that survives is the one with the highest value of the quantity $\beta_i \equiv (k_{a,i}(\alpha_i - \rho_i))/(\gamma_i(k_{d,i} + \rho_i))$, which we interpret as the axon's competitive strength. The activity dependence of β_i means that the most active axon survives provided that the variation due to other factors does not predominate.

3. Compartmental model

We investigate how axonal competition is affected if the extracellular space around the target is not uniform with respect to the concentration of neurotrophin. To this end, we consider two compartments in the extracellular space, each with a single

innervating axon. We deliberately use this simple two-compartment model to demonstrate clearly how competition is affected. Axon i grows in compartment i ($i = 1,2$), in which L_i is the concentration of neurotrophin. Each compartment has volume v_c. The rates of change of C_i and R_i are given by Eqs. (1) and (2), respectively, in which L is replaced by L_i.

Neurotrophin is released in each compartment at rate σ and is removed by degradation with rate constant δ. Between compartments diffusion of neurotrophin takes place. The amount of neurotrophin that flows from one compartment to the other per unit time is approximated by

$$F = -AD\frac{L_2 - L_1}{\lambda}, \tag{5}$$

where D is the diffusion coefficient, A is the cross-sectional area of the compartments, and λ is the distance between the centres of the compartments. The change in the concentrations L_1 and L_2 caused by the flow F will be determined by the volume of each compartment. Adding a diffusion term to Eq. (3), we obtain the rates of change of L_1 and L_2:

$$\frac{dL_1}{dt} = \hat{D}(L_2 - L_1) + \sigma - \delta L_1 - (k_{a,1}L_1R_1 - k_{d,1}C_1)/v_c, \tag{6}$$

$$\frac{dL_2}{dt} = \hat{D}(L_1 - L_2) + \sigma - \delta L_2 - (k_{a,2}L_2R_2 - k_{d,2}C_2)/v_c, \tag{7}$$

where $\hat{D} = (AD)/(\lambda v_c)$.

Eq. (4) again describes axonal growth. The growth function used is $f_i(C_i) = \alpha_i C_i$. Recall that this growth function leads to the survival of only one axon in the model in which the extracellular space is considered to be a single compartment. Parameter values used are as in [11].

4. Results

In contrast to the single-compartment model, in the two-compartment model both axons can coexist. Coexistence occurs for relatively small $\hat{D}$, i.e. if the axons are far apart (large λ) (Figs. 2a–c). In the limit for $\hat{D} = 0$, there is no interaction between the compartments and consequently no competition between the axons.

For relatively large $\hat{D}$, i.e. if the axons are close to each other (small λ), no more than one axon can survive (Figs. 2d–f). In the limit for infinitely large $\hat{D}$, the neurotrophin concentration in both compartments will always be the same, i.e. the model will become effectively identical to the single-compartment model.

We now study exclusion and coexistence using phase plane analysis. Because the rate of change of ϕ_i is of the order of days, we can make quasi-steady-state approximations for the other variables on the time-scale of ϕ_i (i.e. $dC_i/dt = dR_i/dt = dL_i/dt = 0$, $i = 1,2$). Using these approximations, we can draw the nullclines for ϕ_1 and ϕ_2, i.e. the lines depicting the solutions of $d\phi_1/dt = 0$ and $d\phi_2/dt = 0$,

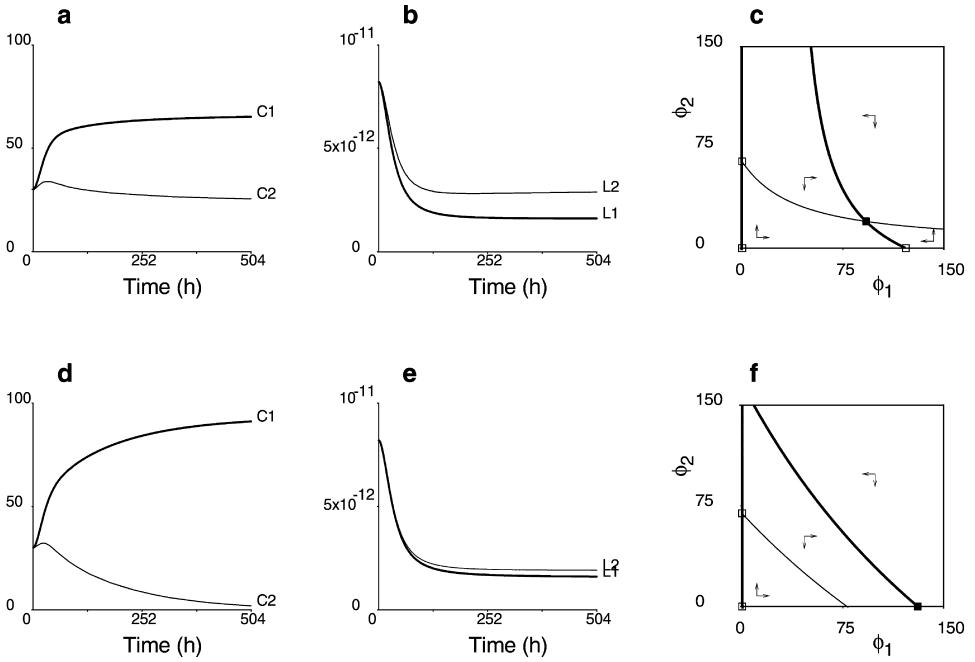

Fig. 2. Coexistence of axons (a–c) and survival of a single axon (d–f) depending on $\hat{D}$. In a–c, $\hat{D} = 0.2$; in d–f, $\hat{D} = 2$. If an axon has no neurotrophin-receptor complex (i.e. $C_i = 0$, equivalent to $\phi_i = 0$), it has died or withdrawn. The values of C_i are in number of molecules; the values of the concentration of neurotrophin, L_i, in mol/l. In c and f, the bold lines are the null-isoclines of ϕ_1, and the thin lines those of ϕ_2. Filled squares indicate stable, and open squares unstable equilibrium points. $\alpha_1 = 1.4$, $\alpha_2 = 0.8$. The values of all the other parameters are the same for both axons.

respectively. The intersection points of the nullclines are the equilibrium points of the system. For $\hat{D} < 0.45$, there is an intersection point where both axons coexist (Fig. 2c). For $\hat{D} > 0.45$, there is no intersection point where both axons coexist (Fig. 2f). Around $\hat{D} = 0.45$, a transcritical bifurcation occurs, where the coexistent equilibrium point disappears.

Spatial separation ($\hat{D}$ small) and coexistence of innervating axons will become possible if the target cell has an extensive dendritic tree. Thus, the larger the dendritic tree, the more innervating axons can survive. If the target cell lacks dendrites, the innervating axons are confined to the relatively small surface area of the soma ($\hat{D}$ large), and only one innervating axon will survive.

5. Discussion

The development of connections between neurons and their targets involves competition among axons for target-derived neurotrophins. To study how the dendritic

tree of the target cell affects the competition, we have formulated a compartmental version of our model of axonal competition [11]. We show that if the innervating axons are spatially near each other on the target, they compete more strongly than if they are further separated, in which case coexistence of axons becomes permissible. Spatial separation of axons is possible if the target cell has an extensive dendritic tree. Thus, the model can account for the finding that in many types of neurons a positive correlation exists between the size of the dendritic tree and the number of innervating axons surviving into adulthood. Although this study does not exclude the role of other factors in axonal competition (such as the form of the axonal growth function [11]), our results emphasize the importance of postsynaptic dendritic morphology in the development of specific patterns of nerve connections.

References

[1] M. Bothwell, Functional interactions of neurotrophins and neurotrophin receptors, Ann. Rev. Neurosci. 18 (1995) 223–253.
[2] S. Cohen-Cory, R.C. Elliott, C.F. Dreyfus, I.B. Black, Depolarizing influences increased low-affinity NGF receptor gene expression in cultured Purkinje neurons, Exp. Neurol. 119 (1993) 165–173.
[3] S. Cohen-Cory, S.E. Fraser, Effects of brain-derived neurotrophic factor on optic axon branching and remodelling in *in vivo*, Nature 378 (1995) 192–196.
[4] L. Garofalo, A. Ribeiro-da-Silva, C. Cuello, Nerve growth factor-induced synaptogenesis and hypertrophy of cortical cholinergic terminals, Proc. Natl. Acad. Sci. USA 89 (1992) 2639–2643.
[5] D.M. Holtzman, Y. Li, L.F. Parada, S. Kinsman, C.-K. Chen, J.S. Valletta, J. Zhou, J.B. Long, W.C. Mobley, $p140^{trk}$ mRNA marks NGF-responsive forebrain neurons: evidence that *trk* gene expression is induced by NGF, Neuron 9 (1992) 465–478.
[6] R.I. Hume, D. Purves, Geometry of neonatal neurones and the regulation of synapse elimination, Nature 293 (1981) 469–471.
[7] D. Purves, J.W. Lichtman, Elimination of synapses in the developing nervous system, Science 210 (1980) 153–157.
[8] D. Purves, R.I. Hume, The relation of postsynaptic geometry to the number of presynaptic axons that innervate autonomic ganglion cells, J. Neurosci. 1 (1981) 441–452.
[9] D. Purves, Body and Brain: a Trophic Theory of Neural Connections, Harvard University Press, Cambridge, MA and London, 1988.
[10] L. Schnell, R. Schneider, R. Kolbeck, Y.-A. Barde, M.E. Schwab, Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion, Nature 367 (1994) 170–173.
[11] A. van Ooyen, D.J. Willshaw, Competition for neurotrophic factor in the development of nerve connections, Proc. R. Soc. B. 266 (1999) 883–892.