第４章：**大脳皮質への調節性入力 Modulatory Inputs to the Cerebral Cortex**

４-１）Introduction

大脳皮質への入力は原則として視床を介して入力しますが、調節性入力 modulatory inputs という特殊な入力に関しては、直接大脳皮質に入力されることが知られています。これらの調節性入力は中枢神経系の多くの組織に入力するのですが、大脳皮質へは以下の調節性神経が入力しています。

（１）indolaminergic inputs: dorsal and median raphe からの **serotonergic inputs**
（２）catecholaminergic inputs
　　青班核からの **noradrenergic inputs**
　　ventral tegmental area (VTA) からの **dopaminergic inputs**
（３）後部視床下部の caudal magnocellular nucleus からの **histaminergic inputs**
（４）前脳基底部 basal forebrain の Meynert's basal nucleus からの **cholinergic inputs**

４-１-１）volume/diffusion transmission

上記の多くの modulatory transmitter は extra-synaptic/ non-synaptic な伝達を行っていると考えられています。これを volume trasnmission あるいは diffusion transmission と言いまして、通常のニューロン連絡に見られる synaptic/ wiring transmittion system と 血流に乗せて全身に分布させ受容体の選択性のみで反応特異性を獲得する endocrine/ hormonal system との中間型に相当します。すなわち、ある程度影響を与える範囲は軸索の投射で決定し、その範囲の中では受容体を持っているニューロンに選択的に影響を与えるという構図になります。

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これら以外にも、活性ペプチドを産生・分泌している皮質ニューロンは多数・多種類あります。これらについても、その伝達様式は volume transmission であろうと推測されます。

錐体細胞の産生するペプチド：
　　CCK
抑制性ニューロンの産生するペプチド：
　　substance P, cortistatin, enkephalins
　　somatostatin, neuropeptide Y
　　VIP, CCK, CRF, dynorphins, neurokinin B (neuromedin K)

また、グルタミン酸や GABA であっても、metabotropic glutamate receptor や GABA-B receptor に作用する時は、これらの受容体が postsynaptic site に限局していないことが多く、non-synaptic transmission である可能性が高くなります。こちらの場合は通常シナプス部位で分泌される物質ですので、シナプスから spill-over して non-synaptic 受容体にたどり着くと考えます。ただ

し、glutamate はアストログリアによる取り込みが盛んなので、そう遠くまで拡散できないと考えられます。

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4-2）serotonergic inputs

セロトニン作動性ニューロンから皮質への入力は古くは、Falck、Hillap 等の histochemical technique (Falck-Hillap法と呼びました) で報告されていました (Fuxe, 1965a, 1965b; Olson et al 1973)。

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4 - 4) noradrenergic input

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4 - 4 - 1) adrenergic receptors

4 - 5) dopaminergic input

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4-7-1） muscarinic receptors

4-7-2） nicotinic receptors

4-8） Chemically specific connections of modulatory inputs to cortical neurons 皮質ニューロンへの調節性神経入力

現時点で、一般的に神経結合が形成されるときのイメージは

（１）胎児期に軸索が進展してどの方面の神経核あるいは皮質に向かうか決めるときには、誘因因子・反発因子などを利用した molecular basis の過程が主として働く。これは主に遺伝子発現により、実行される。

（２）出生後の臨界期あるいは個体の成熟後には、どのニューロンが実際の神経結合を作り、局所のネットワークを決めるかということについては、ランダムファクターが重きをなし、経験依存的・活動依存的になされる。

というように考えられています。

しかし、一部の神経結合においては、経験依存的・活動依存的ではなく、化学的に、すなわち遺伝子発現により決まっているように見受けられるものが散見されます。ここでは大脳皮質におけるそういった Chemically specific connection を紹介しましょう。

他の中枢神経組織と同じように、大脳皮質へは多種類の調節性神経が入力しています。

（１）indolaminergic inputs: dorsal and median raphe からの **serotonergic inputs**
（２）catecholaminergic inputs
　　青班核からの **noradrenergic inputs**
　　ventral tegmental area (VTA) からの **dopaminergic inputs**
（３）後部視床下部の caudal magnocellular nucleus からの **histaminergic inputs**
（４）前脳基底部 basal forebrain の Meynert's basal nucleus からの **cholinergic inputs**

これらの入力は diffusion/volume transmission を主としますので、特異性は受け手側のニューロンに発現する受容体次第であることは明らかです。しかし、これらの入力がシナプス結合を作る時には入力先の皮質ニューロンを選んでいる可能性が高いことが知られています。また、シナプス結合をなす場合、これらの調節性入力が glutamate/GABA などを cotransmission している可能性も高くなります。例えば 5HT 入力などでは synaptic には glutamatergic であることも考えられます。

４-８-１）**Serotoninergic inputs to GABAergic neurons**

皮質への調節性神経入力のうち、一番最初にその target specificity が報告されたのはセロトニン作動性入力でした [Hornung & Celio 1992]。5HT fibers は marmoset の皮質に diffuse に分布していますが、その一部が、L1-3 で pericellular array (basket) を形成しており、その中身は錐体細胞ではなく、GAD+/CB+/PV– な interneuron であるとされました。その後、サルの prefrontal cortex でも axodendritic (shaft) asymmetric synapses の相手は主として aspiny な interneuron であり、錐体細胞の shaft は 8% しかないことが報告されました [Smiley & Godlman-Rakic 1996]。なお、5HT+ varicosities の 23% しか asymmetric synapse を形成しておらず、基本的には volume transmission をしているのであろうことも確認されました。ラットの V1 では basket 形成は認められないものの、axo-somatic/axo-proximodendritic synapses の相手は SS+/NPY+/VIP– interneuron であることが確認され、CB+ interneuron も SS+/NPY+/VIP– interneuron も group II GABAergic neuron に属することから marmoset の結果と矛盾しないことが指摘されました [Paspalas & Papadopoulos 2001]。

一方、サルとヒトの新皮質の L2/3 の錐体細胞の axon initial segment (AIS) に 5HT1A 受容体が集積しています [DeFelipe et al 2001]。しかもこれらの部位は PV+ chandelier axon で囲まれていました。したがって、この部位での 5HT の作用は non-synaptic であり、5HT の影響が interneuron に限局されていないことを意味します。

Hornung J-P, Celio MR (1992) The selective innervation by serotoninergic axons of calbinidin-containing interneurons in the neocortex and hippocampus of the marmoset.
Smiley JF, Goldman-Rakic PS (1996) Serotonergic axons in monkey prefrontal cerebral cortex synapse predominantly on interneurons as demonstrated by serial section electron microscopy.
DeFelipe J, Arellano JI, Gómez A, Azmitia EC, Muñoz A (2001) Pyramidal cell axons show a local specialization for GABA and 5-HT inputs in monkey and human cerebral cortex. J Comp Neurol. 2001 Apr 23;433(1):148-55.
Paspalas CD, Papadopulos GC (2001) Serotninergic afferents preferentially innervate distinct subclasses of peptidergic interneurons in the rat visual cortex. Brain Res 891: 158-67.

４-８-２）Dopamine (catecholamine) input to cortical GABAergic neurons and pyramidal neurons

始めに Goldman-Rakic ら [1989] はサルの新皮質錐体ニューロンに DA+ or TH+ terminal が symmetric synapse を形成して入力することを報告しましたが、その後サルの prefrontal cortex (PFC) で、固定後 LY intracellular injection 法を用いて、90 TH+ appositions / L3 pyr cells の入力を見ており、その密度は 7-8/mm (L3), 14/mm (L2) で、L5, L6 でもほぼ同一密度でした [Krimer...Goldman-Rakic 1997]。一方で 非錐体細胞にはこの半分の密度 (5.3/mm in L2; 4/mm in L3) でした入力していませんでした。これらの結果は DA 入力は錐体細胞を好んでいることを意味しました。

一方、ラットの medial PFC (mPFC) で、DA-immunoeractivite (ir) bouton が GABA+ interneuron cell body に頻繁にappose していることが報告されました [Benes et al 1993]。L6 では、錐体細胞の 71%, 非錐体細胞の 76%, GABA+ 細胞の 65% が DA+ inputs を受けていました。平均して、30% の DA+ bouton が GABA+ 細胞に入力しており、ランダムな入力を仮定した場合よりは比べて好んで入力することが指摘されました。次に、ラットの mPFC L5/6, サルの PFC L1-4, M1L1-4 で、DA+ or TH+ inputs の相手を見た仕事があります [Sesack et al 1995]。synapse を形成している場合は全て symmetric でしたが、GABA+ dendrites, GABA– dendrites ともに入力していました。彼らはさらにサルの PFC L3b-4 で、TH+ terminal が PV+ dendrites に入力しましたが、L1-3b では少なかったことを見ています [Sesack et al 1998]。さらに彼らは、ラット PFC で TH+ terminals が Accumbense nucleus に投射する錐体細胞に終止していることを報告しました [Carr ... Sesack 1999]。

＊ TH ir を使用している場合、dopaminergic か noradrenergic かを区別できていないという問題点があります。

Goldman-Rakic PS, Leranth C, Williams SM, Mons N, Geffard M (1989) Dopamine synaptic complex with pyramidal neurons in primate cerebral cortex. Proc Natl Acad Sci U S A. 1989 Nov;86(22):9015-9.
Benes FM, Vincent SL, Molloy R (1993) Dopamine-immunoreactive axon varicsities form nonrandom contacts with GABA-immunoreactive neurons of rat medial prefrontal cortex. Synapse 15: 285-95.
Sesack SR, Snyder CL, Lewis DA (1995) Axon terminals immunolabeled for dopamine or tyrosine hydroxylase synapse on GABA-immunoreactive dendrites in rat and monkey cortex. J Comp Neurol 363:264-80.
Krimer LS, Jakab RL, Goldman-Rakic PS (1997) Quantitative three-dimensional analysis of the catecholaminergic innervation of identified neurons in the macaque prefrontal cortex. J Neurosci 17: 7450-61.
Sesack SR, Hawrylak VA, Melchitzky DS, Lewis DA (1998) Dopamine innervation of a subclass of local circuit neurons in monkey prefronal cortex: ultrastructural analysis of tyrosine hydroxylase nad parvalbumin immunorective structures. Cerebral Cortex 8: 614-22.
Carr DB, O'Donnell P, Card JP, Sesack SR (1999) Dopamine terminals in the rat prefrontal cortex synapses on pyramidal cells that project to the nucleus accumbense. J Neurosci 19:11049-60.

４-８-３）Noradrenergic (NA) inputs to cortical GABAergic neurons

NA-ir varicosities は SS+, NPY+, VIP+ neurons に入力していました [Paspalas & Papadopoulos 1999]。とくに、NPY+ cell body、そして頻度は少なくなるものの SS+ cell body にpericellular array として入力していました。しかし、VIP+ cell では pericellular array を作らず、single terminal の入力でした。電顕的には symmetric synapses を形成していました。

＊NA と DA の抗原としての違いは少しですので、anti-NA antibody の特異性はどの程度あるのかちょっと不安になります。NA の合成酵素 dopamine-beta-hydroxylase (DBH) の免疫染色の所見と比べたくなります。

Paspalas CD, Papadopulos GC (1999) Noradrenaergic innervation of peptidergic inerneurons in the rat visual cortex. Cerebral Cortex 844-53.

４-８-４）Basal forebrain cholinergic inputs to cortical GABAergic neurons

Vaucher E, Linville D, Hamel E (1997) Cholinergic basal forebrain projections to nitric oxide synthase-containing neurons in the rat cerebral cortex. Neuroscience 79:827-836, reprint(+), ID = 4150

４-８-５）Basal forebrain GABAergic inputs to cortical GABAergic neurons

Basal forebrain (DBB 中心に PHA-L 注入) の GABAergic corticopetal projection neurons からの入力は、cingulate, retrosplenial > frontal, occipital areas に投射しましたが、主に en passant type で、その多くが GABA+ symmetric synapse を形成します [Freund & Gullyas 1991]。en passant type は mesocortex L1, L4 に、neocortex L4 > L5, L6 >> L2/3 に分布していまして、受け手の interneuron としては SS+ or CB+ cell が多く、小数の PV+ cell にも入力していました。

Freund TF, Gulyás AI (1991) GABAergic interneurons containing calbindin D28K or somatostatin are major targetes of GABAergic basal forebrain afferents in the rat neocortex. J Comp Neurol 314: 187-99.