Regulation of Neuromodulator Receptor Efficacy - Implications for Whole-Neuron and Synaptic Plasticity

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Abstract

Membrane receptors for neuromodulators (NM) are highly regulated in their distribution and efficacy - a phenomenon which influences the individual cell's response to central signals of NM release. Even though NM receptor regulation is implicated in the pharmacological action of many drugs, and is also known to be influenced by various environmental factors, its functional consequences and modes of action are not well understood. In this paper we summarize relevant experimental evidence on NM receptor regulation (specifically dopamine D1 and D2 receptors) in order to explore its significance for neural and synaptic plasticity. We identify the relevant components of NM receptor regulation (receptor phosphorylation, receptor trafficking and sensitization of second-messenger pathways) gained from studies on cultured cells. Key principles in the regulation and control of short-term plasticity (sensitization) are identified, and a model is presented which employs direct and indirect feedback regulation of receptor efficacy. We also discuss long-term plasticity which involves shifts in receptor sensitivity and loss of responsivity to NM signals. Finally, we discuss the implications of NM receptor regulation for models of brain plasticity and memorization. We emphasize that a realistic model of brain plasticity will have to go beyond Hebbian models of long-term potentiation and depression. Plasticity in the distribution and efficacy of NM receptors may provide another important source of functional plasticity with implications for learning and memory.

Key words: neuromodulators, G-protein coupled receptors, regulatory networks, neural signal transmission, learning, sensitization, dopamine, metaplasticity, LTP, synaptic plasticity

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1 Introduction

G-protein coupled receptors (GPCRs) which comprise a major group of cellular receptors on many types of cells, including neurons, undergo significant plasticity.

GPCRs become desensitized (phosphorylated) as a form of short-term plasticity, which means that receptors are temporarily uncoupled from their effectors (G-proteins). They also become down- or upregulated in a more lasting form of plasticity, which involves receptor trafficking between intracellular stores and the cell membrane, and in some cases receptor degradation as well as new protein synthesis. These processes affect receptors for the main neuromodulators serotonin, dopamine, noradrenaline and acetylcholine, for neuropeptides such as opioids, for neurohormones such as steroids or estrogen, as well as the metabotropic glutamate (mGLU) and $GABA_B$ receptors in the brain.

In general, receptors are sensitized and desensitized in response to agonist exposure, modulated by cell internal parameters and synaptic activation. Important parameters for receptor plasticity are cell-internal calcium, and the second-messenger dependent protein kinases A and C (PKA and PKC), as well as G-protein specific kinases (GRKs). The time-scale of these changes is within minutes for desensitization and several hours for alterations in receptor distribution, which is comparable to 'early' and 'late' long-term potentiation.

The functional significance of this adaptive regulation is at present not well understood. Receptor regulation has mainly be studied in response to various pharmacological agents (antipsychotics, antidepressants, drugs of abuse), where sensitization of NM responses has consistently been shown in different tissues and cell types (e.g. ventral tegemental area and nucleus accumbens) (1; 2). Behavioral effects of stress (3), learning (inhibitory avoidance, (4; 5; 6)), and environment (novelty, social conditions) have also been documented (7; 8).

This evidence which points at an experience-dependent regulation of NM receptors coexists with a significant body of data showing constitutive expression of receptors to different types of neurons. The level of receptor expression varies for projection neurons (cortical pyramidal cells or striatal medium spiny projection neurons) vs. local interneurons (fast-spiking vs. regular spiking neurons) (9; 10), for different cortical layers or for patches in amygdala or striatum (5), according to neuropeptide colocalization (e.g., substance P, enkephalin) (11), and for neurons with a different connectivity (striato-nigral vs. striato-pallidal neurons) (12). There is also developmental regulation of receptor expression which is different postnatally (13; 14), during adolescence (15; 16), as well as during ageing (17).

Constitutive receptor distribution sets the boundaries within which experien-

ce-dependent fluctuations occur. These fluctuations may be *transient* or they may have a *permanent* component corresponding to short-term desensitization and long-term down- or up-regulation. In this paper we provide an overview of the biological mechanisms involved in NM receptor regulation with the goal of analyzing the adaptive function of this process. We will find that receptor efficacy undergoes significant changes that are important in mediating neuromodulatory signals. We will also find that the regulatory processes underlying receptor plasticity are partly overlapping with the processes underlying LTP/LTD.

We suggest that NM receptor regulation is a process which has the capacity to contribute to brain plasticity on the population level, on the level of the individual neuron and probably also on the level of the synapse. This provides a mechanism for memorization and an added storage capacity beyond Hebbian long-term potentiation and long-term depression. A better insight into the role of NM receptor regulation may lead to a new understanding of brain plasticity and a thorough revision of current theories of memory and learning.

2 Protein Regulatory Networks Underlying Receptor Plasticity

2.1 Component processes of receptor regulation

The molecular biology of receptor regulation has been elucidated in considerable detail, mostly by studies on cultured cells stably transfected with receptors at fixed concentrations.

A number of different components have been identified:

(1) conformational change of receptor protein and functional uncoupling from effectors (G-proteins) by **phosphorylation**.
(2) translocation of receptors from the membrane to a cytoplasmic structure (in endoplasmic reticulum and Golgi apparatus) (**receptor internalization**).
(3) reduction in potency and efficacy of a receptor in inducing changes in second-messenger concentration (adenylyl cyclase, cAMP) (**desensitization**).
(4) **receptor degradation** in lysosomes, which removes receptor proteins from the cytoplasma as well as the plasma membrane.
(5) translocation from a pool of internally stored receptors to the membrane (**recruitment**, resensitization).
(6) delivery of newly synthesized receptors to the membrane (**protein synthesis**).

This shows that receptor regulation is far from being a simple process, as might be expected if homeostatic regulation by feedback control were its only function. Rather, the "layering" of several processes indicates that both short-term and long-term regulation of receptors occurs and that different "entry-points" for interacting processes exist to influence the outcome of a specific stage in receptor regulation.

The prototype case for GPCR regulation has been the regulation of the β-adrenergic receptor (18; 19), but the processes involved are somewhat different for each individual GPCR type. We focus here on the dopamine D1 receptor, which is also well documented, and which is of considerable significance in the regulation of membrane excitability and neural signal transmission.

2.2 Protein regulatory network

The specific proteins and signalling substances involved in receptor regulation are shown as a regulatory network for the dopamine D1 receptor in Fig. 1.

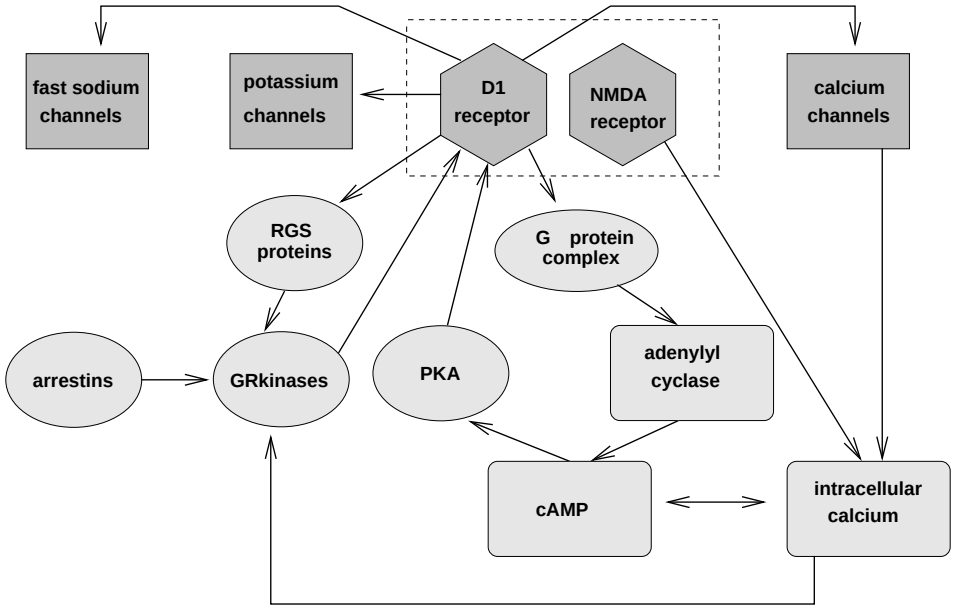

Fig. 1. D1 receptor effectors and regulators: dark shaded, membrane receptors and ion channels, light shaded, intracellular pathways. Possible dimerization D1-NMDA is shown. Note the direct feedback regulation via PKA, also via RGS, GRK and the indirect regulation via calcium, GRK. Possible interactive effects between cAMP and Ca are also shown.

Functional D1 receptors are coupled to G-proteins, which form heterotrimeric complexes. When receptors become activated, the coupled G-proteins dissolve into two components: G_α and $G_{\beta\gamma}$. These components have the ability to modulate a number of membrane ion channels, such as inwardly rectify-

ing K+ channels (e.g. GIRK channels) (20), I_h and other K+ channels (21), high-voltage gated calcium channels (L-type, P/Q/R-type and N-type calcium channels) (22; 23), and also sodium channels (24; 25). D1 receptors furthermore have the effect of increasing NMDA transmission (26; 27), and may have complex effects on local calcium levels (28).

D1 receptors communicate with cell-internal pathways by activating G_{olf}-proteins (29), which raise adenylyl cyclase and cAMP-levels. cAMP-levels and calcium levels are required for the activation of the transcription factor CREB and the 'early genes' fos and delta-fosB. Both proteins regulate the translational activity of mRNA and are critically involved in new protein synthesis. D1 receptor coupling is reduced by protein kinases - both cAMP-dependent kinase PKA and G-protein specific kinases (GRKs) (18; 30). These kinases phosphorylate the receptor protein and contribute to the desensitization of its effect on second messengers. Calcium indirectly reduces desensitization, via the calcium-dependent protein calmodulin, which inhibits GRKs (31). Another pathway for calcium to prevent desensitization has recently been detected in the calcium sensor NCS-1, which reduces phosphorylation and internalization of the D2 receptor (32). Arrestins can increase the effects of GRKs, for instance, overexpression of arrestins reduces the ability of β-adrenergic receptors to activate G_S by $> 75\%$ (33). They play a major role in the internalization of receptors.

Desensitization is furthermore influenced by RGS-proteins, which regulate G-proteins and G-protein signaling by activating GTPase (34; 35; 36). GTPase is the kinase which phosphorylates G-proteins, and renders them insensitive to receptor activation. RGS proteins take part in producing fast kinetics in vivo by favoring reformation of the heterotrimeric state (G_α + $G_{\beta\gamma}$), while the hydrolysis of GTPase is 40-fold slower in the absence of RGS (34). The effect of overexpression of RGS proteins is a change in kinetic rate, an acceleration of the desensitization-resensitization cycle and also a net decrease of desensitization. RGS levels themselves may become upregulated by dopamine D1 and D2 activation e.g. in striatum, specifically RGS-2 and RGS-4 seem to be enhanced by D1 or D2 receptor activation respectively (37; 38).

3 Short-Term Desensitization of Receptors

3.1 Receptor phosphorylation and desensitization of second-messenger activation

Receptor efficacy in general is determined by the amount of functional coupling of an agonist and the reactivity of effector pathways.

Receptor phosphorylation and internalization affect signal transduction by agonist binding as a form of short-term variation. Membrane receptors undergo functional decoupling by phosphorylation at multiple Ser and Thr residues, which induces conformational change of the protein and prevents effective ligand binding (39; 40). Phosphorylation is fast, with a half-time of less than a minute for the D1 receptor and it is also reversible upon agonist removal with a half-time for resensitization of about 10-15 minutes for the D1-receptor (41; 42), cf. (43).

Phosphorylation and internalization may be achieved by PKA, which is cAMP-dependent, or by GRKs, which are subject to regulation by calcium via calmodulin or NCS-1 (44; 45; 46). Calcium may enhance receptor efficacy, when intracellular calcium binds to calmodulin, and inhibits GRKs, e.g. GRK5 (46). Interestingly, there may be another, "corrective", pathway for a direct interaction between calcium and GRK: the inhibition of GRKs by calmodulin can be abolished by high levels of (calcium-dependent) protein kinase C (PKC) (47). In general, overexpression of GRKs leads to reduced functional coupling and requires more agonist to achieve the same amount of effect on second messengers (subsensitivity) (48; 49; 50).

The role of PKA in phosphorylation of the D1 receptor is to a certain degree controversial (51). There is indirect evidence from cell lines with reduced PKA activity where desensitization is attenuated (52), and from mutant receptors which lack a PKA phosphorylation site, where the onset time of desensitization is greatly reduced (39). Also, (53) and (54) show that stimulating PKA can mimic agonist-dependent desensitization. But there are also data by (55; 56), which seem to indicate that PKA is not important in desensitization. The work by (40) (based on a PKA-insensitive mutant receptor) suggests that PKA has a major effect on receptor trafficking within the cell and increases proteolysis, but is not strictly required for desensitization of cAMP. Thus it has been suggested that PKA modifies a later process in desensitization, which is more intimately linked to internalization and recycling probability, rather than agonist-induced phosphorylation. In this sense, GRKs and PKA are most effective at different stages of the desensitization process. This would also imply a different time course of their feedback regulation, since PKA would operate with a longer delay in its reduction of receptor efficacy.

3.2 Key factors in desensitization

When a receptor is in a phosphorylated state, it is effectively uncoupled from its effectors, until it becomes dephosphorylated. For the dopamine D1 receptor, both of these processes can be performed without internalizing the receptor. However internalization is often the consequence of phosphorylation and both

processes together may be termed "desensitization", since they affect the functional efficacy of a receptor population in transmitting signals to intracellular pathways.

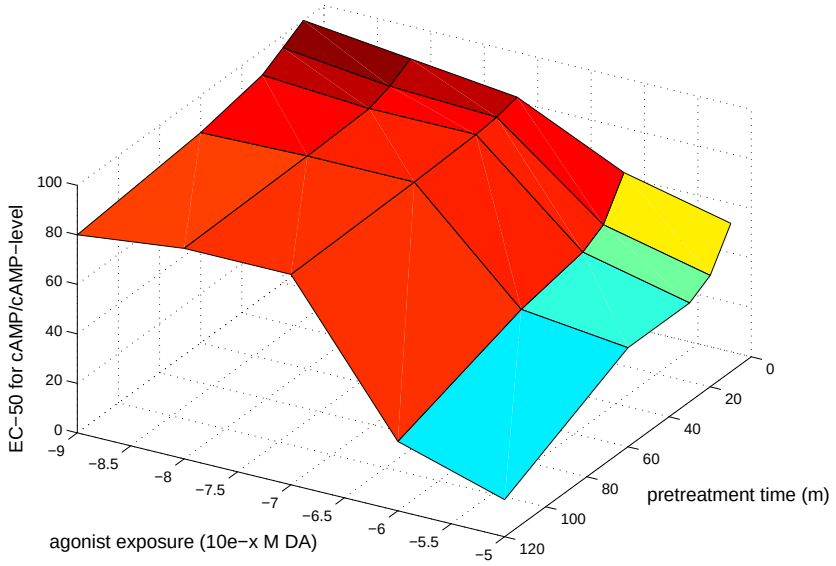

Fig. 2. Desensitization of the cAMP pathway for the D1 receptor. Data have been combined from (57), (41) and (55). The sigmoid shape of the dose-response relationship is clearly evident in the vertical axis. Length of pretreatment in contrast seems to follow a logarithmic curve. The reduction of efficacy can reach up to 80%.

To study the desensitization mechanism for a given receptor, receptors are overexpressed in cultured cells, and then exposed to agonists at different concentrations and for different times. The amount of functional coupling is assessed by measuring concentrations of adenylyl cyclase or cAMP. These experiments have shown that functional efficacy strongly depends on the level of agonist exposure.

Fig. 2, 3 show the time course of desensitization by measuring the concentration of adenylyl cyclase and cAMP. In Fig. 2 data from (57), (41) and (55) are combined. The desensitization of the D1 receptor reduces the ability of a brief dopamine challenge to enhance adenylyl cyclase and cAMP-levels. This desensitization is both dose-dependent and dependent on pretreatment time. Dose-dependence follows a sigmoidal shape, with a critical range between 10^{-6} and 10^{-7} mol dopamine. Pretreatment time does not increase desensitization much beyond an initial effect. Overall, there is a reduction in receptor efficacy of up to 80%.

Fig. 3 shows similar data from the desensitization of the D2 receptor (58). The D2 receptor has the capacity to inhibit the adenylyl cyclase/cAMP pathway and this capacity is reduced by agonist-dependent desensitization only up to 20%. The critical range of agonist exposure, however, is similar. Again,

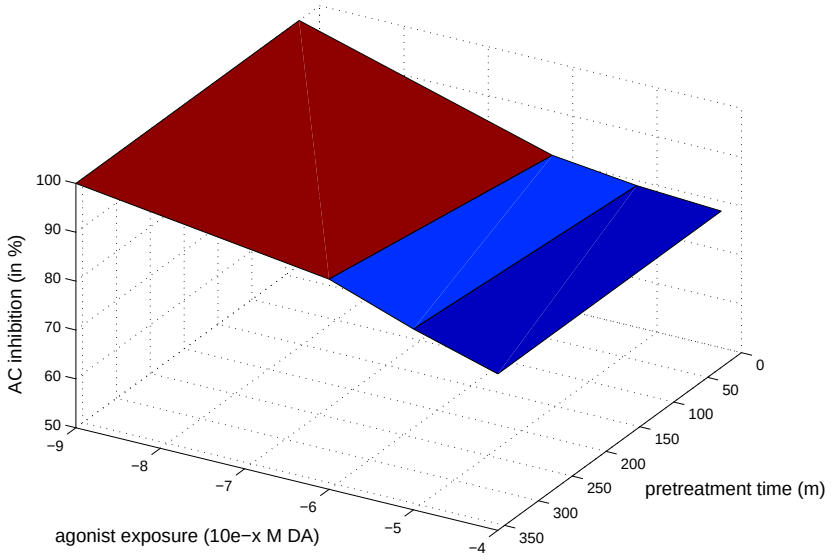

Fig. 3. Desensitization of adenylyl cyclase(AC) inhibition for the D2 receptor. Data are taken from (58). Possibly sigmoidal and logarithmic shapes of the curves are less evident, probably as a result of the limited data set. The effect of desensitization is limited to about 20%.

pretreatment time (here up to 6 h) is not a strong factor.

We can derive a general functional form for receptor efficacy (C) which reflects the dependence on agonist stimulation (A):

$$C = \frac{1}{1 + e^{-A}}. \tag{1}$$

The amount of agonist stimulation can be described by an integral over the NM concentration:

$$A = \int NM_t dt. \tag{2}$$

The sigmoidal shape of the function reflects the fact that receptor efficacy is almost linearly dependent on agonist exposure within a certain concentration range and reaches saturation or stays below a threshold otherwise. This is visualized in Fig. 4. Furthermore, Fig. 4 shows the modification of this basic shape by additional parameters (s. below).

It may well be that receptor desensitization depends on the particular time course of agonist exposure rather than the total amount. These experiments, though technically feasible, have not systematically been carried out. For instance, phasic increases of NM concentrations which are short-lasting may fail to desensitize receptors significantly, while tonic increases with a smaller total amount of agonist stimulation may have a larger effect. However, in the absence of experimental data, integrating over agonist concentrations in time

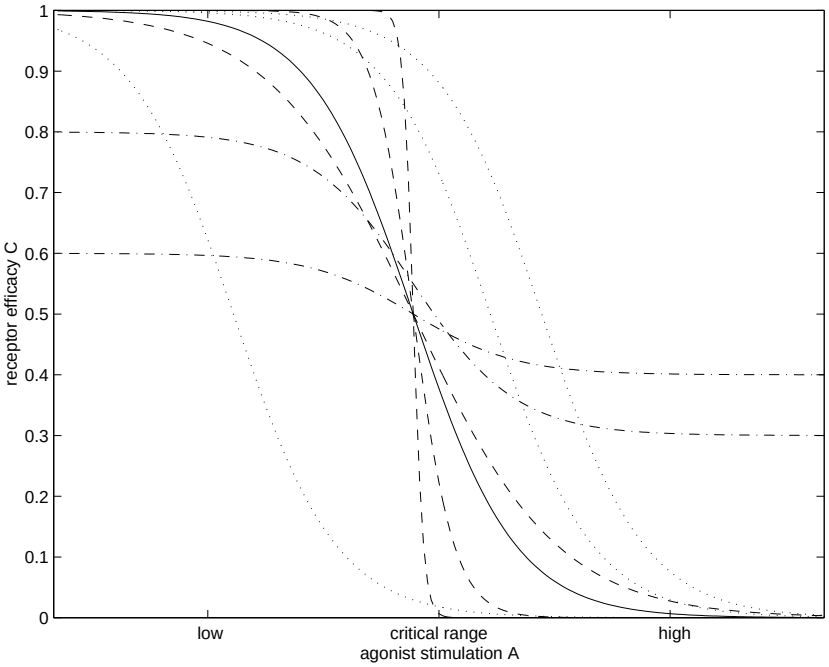

Fig. 4. General form of NM receptor efficacy and its variability by parametrization. Dotted lines (. . .) show shifts in dose-dependence (I_1), dashed lines (- -) correspond to the rate of desensitization (I_2), dashed-dotted lines (-.) correspond to the degree of agonist-dependence (λ).

seems to be the best approximation. Further work may allow to refine the formula in eq. 2 to incorporate different temporal patterns of agonist stimulation.

This basic agonist-dependent desensitization may be modified by a number of factors. First of all, as we have seen, there are several cell-internal parameters which influence the magnitude of desensitization. For instance, a high level of GRKs shifts the agonist-dependence curve to the right (48; 49; 50). A basic parameter I_1 allows to express sub- and supersensitivity of receptors, defined by dose-dependence of agonist exposure:

$$C = \frac{1}{1 + e^{-A+I_1}}. \tag{3}$$

Presumably, the amount of phosphorylation by protein kinases can be expressed with this parameter. Experimental data show that I_1 can be manipulated by overexpression of GRK (50). We'd similarly expect increased calcium/calmodulin to have an effect on this parameter.

The action of RGS proteins is different in that it has a significant effect on the resensitization dynamics. Receptors prompt conversion of the inactive G protein to an active form. RGS proteins accelerate the conversion of the activated G protein back to its inactivated form (35; 36). Several studies have shown

(59; 34) that reduced RGS activity leads to significantly less receptor efficacy both in terms of slow onset and prolonged recovery times, measured by N-type calcium channel or GIRK channel activity (see Fig. 5). In contrast, high RGS levels lead to fast recovery and may reduce onset of receptor activation (60; 61; 62; 63).

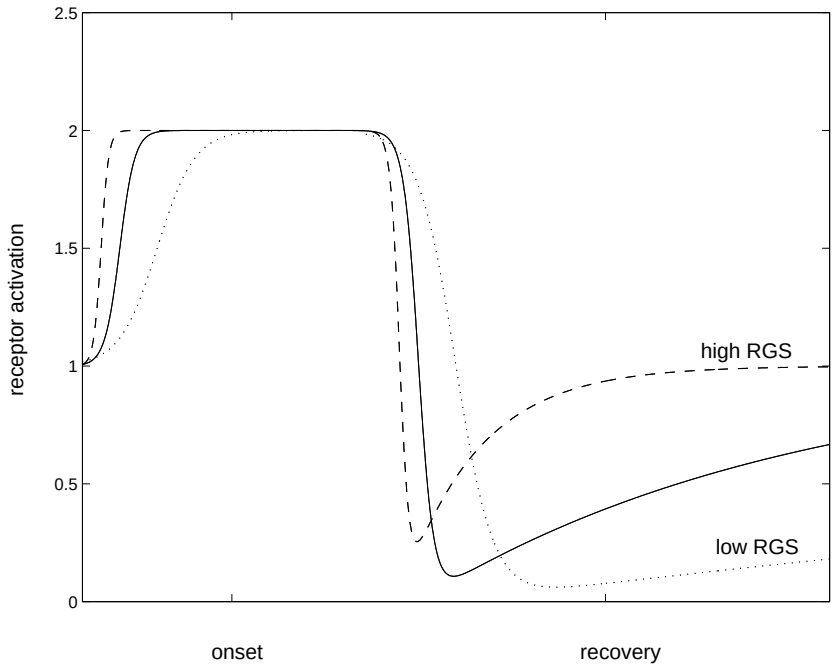

Fig. 5. Desensitization dynamics modulated by RGS-proteins. The functional shape is adapted from (34) and (60), according to alterations in the half recovery time $t_{0.5}$ and the rise time t_{rise}.

Thus RGS proteins speed up resensitization and affect receptor efficacy independent of agonist levels. This effect can be expressed by a parameter I_2:

$$C = \frac{1}{1 + e^{\frac{-A+I_1}{I_2}}}. \tag{4}$$

Finally, desensitization depends on the amount of time a receptor exists in the functional conformational state. Receptors may exhibit a high degree of spontaneous conformational change, which means that they become activated even in the absence of agonist binding. For dopamine receptors, D5 receptors, which are similar to D1 receptors, have a high degree of this constitutive activity (64), cf. (65; 66). This can be expressed by a factor for desensitization (λ) which is constitutive for each receptor type.

$$C = \lambda \frac{1}{1 + e^{\frac{-A+I_1}{I_2}}}. \tag{5}$$

Receptor efficacy as measured by effects on cAMP/adenylyl cyclase need not be identical to effects on membrane ion channels and consequently neural transmission. But in general, dopamine D1 mediated effects on membrane excitability can be mimicked by forskolin-mediated stimulation of PKA, implicating the cAMP-pathway as the major factor in regulating membrane properties. The cAMP/adenylyl cyclase pathway thus provides an important state parameter for the regulation of protein phosphorylation, the expression level of protein kinases and a common pathway for a number of G-protein coupled receptors. Strictly synaptic components of receptor activation (NMDA channel regulation and presynaptic regulation of transmitter release), however, may be regulated by other pathways, with prominent dependence on calcium and protein kinase C levels. The cAMP-pathway also influences early gene expression (c-fos, delta-fosB, CREB), which are important variables for protein synthesis and any functional cell plasticity that is regulated in the long-term. Thus we can regard regulation of the cAMP pathway as a basic mechanism that may affect receptor efficacy for both membrane excitability and gene expression/ protein synthesis (cf. (67; 41)). The relation between receptor efficacy and synaptic modulation may be regulated in a somewhat different way.

We have seen that the efficacy of the D1 receptor in raising intracellular cAMP-levels depends on the influence of different factors on the desensitization function.

Three different types of parameter (λ, I_1, I_2) can be distinguished by their influence on receptor efficacy (see Fig. 4).

I_1 shifts the function to the left or right without affecting its shape, corresponding to an alteration of the dose-response relationship.
I_2 alters the steepness of the function and thus the temporal properties of receptor desensitization.
λ flattens the curve indicating less dependence on agonist stimulation.

This basic variability of receptor efficacy emerges from the parametrization of the functional form. Parameter fitting to experimental data may allow a further quantitative analysis of these functional relations.

3.3 Feedback loops in regulating receptor efficacy

In this section, we will outline a model for the dynamic interactions that determine receptor efficacy. We will develop a qualitative approach that demonstrates the emergence of bistability in receptor efficacy - understood here as a stable state which results from a prolongation of the cellular response beyond the actual duration of the signal. In a slightly different sense, bistability emerges when there are trigger signals both to induce a new state and to turn

$$V_{PKA} = \alpha_1\ I_{PKA} + \beta_1\ V_{NM}$$
$$V_{RGS} = \alpha_4\ I_{RGS} + \beta_4\ V_{NM}$$
$$V_{Ca} = \alpha_3 I_{Ca} + \beta_3\ V_{NM}$$
$$V_{GRK} = \alpha_2 I_{GRK} - \beta_2\ V_{Ca}$$
$$I_1 = -\gamma_1\ V_{PKA} - \gamma_2\ V_{GRK} + \gamma_3 V_{RGS}$$
$$I_2 = \gamma_4 V_{RGS}$$
$$A = \textstyle\sum_{t=0} I_{NM}$$
$$C = 1/(1 + e^{(-A+I_1)\ 1/I_2})$$
$$V_{NM} = C\ I_{NM}$$

Table 1
A system of equations defines a simulation model for the regulation of receptor efficacy C. Concentrations for PKA, Ca and RGS (V_x) are determined by an independent component I_x and by feedback from the receptor activation V_{NM}. GRK is determined by I_{GRK} and the calcium level V_{Ca}. λ is regarded as a fixed parameter for the D_1 receptor. The actual receptor activation V_{NM} is modeled as a product of agonist concentration and receptor efficacy.

it off (cf. (68; 69; 70) for discussions of bistability and multistability in this context), and as we shall see this condition is probably also met. The model is purely qualitative, an attempt to illustrate the conditions that might underlie a short-term regulation of receptor efficacy that provides an important physiological state parameter for understanding the computational properties of neuromodulation. But a full numerical model, e.g. based on chemical mass-action models (71; 72) could be developed on the basis of this approach and would allow more detailed investigations of these interactions.

The model determines the parameters I_1 and I_2 in eq. 5 from kinase activity (I_1) and RGS-level (I_2). The protein regulatory interactions that determine the parameters I_1 and I_2 in this model are described by a number of equations as shown in Table 1. Each of the concentrations in the model is calculated from a component that is independent of feedback within the system (I_{Ca}, I_{PKA}, I_{GRK} and I_{RGS}), and a component that depends on the activation of the receptor (V_{NM}). GRK levels specifically are influenced by indirect feedback via calcium levels - which provides an entry-point for a more complex regulation of GRK levels by other processes affecting calcium. The ratio between these components is determined by the factors α_i and β_i. This analytical approach of separating system-internal components from outside influences has clear advantages in model construction and control over system components and also enables modular construction with clearly defined interfaces which is lacking

in more 'bottom-up' approaches to intracellular modeling (72; 73).

However, it is assumed that the effect of the receptor activation V_{NM} on the concentration is only linear - raising or lowering levels by an amount proportional to V_{NM}. This is a simplifying assumption that may have to be examined in further work.

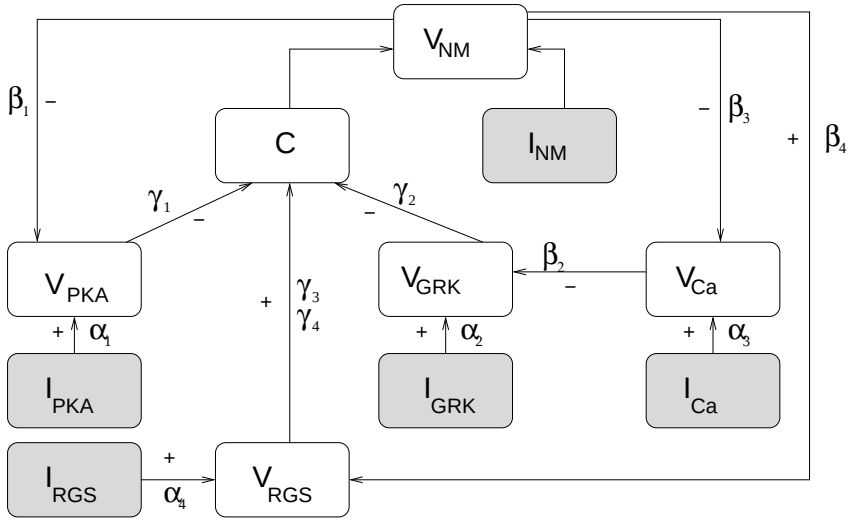

Fig. 6. The diagram shows the dependencies between the concentrations for the kinases GRK and PKA, for calcium, and the role of RGS proteins. The factors α_i, β_i and γ_i are shown as labels on the links between parameters.

Fig. 6 visualizes the relations between the parameters. The target regulated value is the receptor efficacy C. The actual receptor activation effect V_{NM} is defined by both the efficacy C and the current agonist stimulation I_{NM}. The main parameters I_1 and I_2 are defined by concentrations of the kinases PKA and GRK (V_{PKA} and V_{GRK}), and the levels of RGS-proteins (V_{RGS}). Specifically, I_1, which determines the right- or left shift of the dose-response curve for the receptor, is assumed to be a linear combination of the concentrations for the two kinases. Since these kinases may act with different time courses, a more complex interaction may have to be empirically determined by more detailed experimental work.

C is being set by the agonist exposure summed over time, and indirectly by the PKA, GRK and RGS levels. There is also some experimental evidence concerning the free parameters α_i, β_i and γ_i in the system. For instance, the ratio β_1/α_1 should be larger than β_3/α_3. This is the case, since the contribution of D1 receptor activation to PKA levels is probably much higher than its contribution to calcium levels (28; 57; 41; 55). Also, $\gamma_2 > \gamma_1$, since GRK seems to have a stronger effect than PKA on receptor regulation (see above, section 3.1).

With this system we arrive at a simplified, but functional model for the com-

putation of receptor activation, taking the internal state of the neuron, defined by protein and calcium concentrations, into account. Further work is needed to more fully develop such a model as a basis for empirical predictions and in close correspondence with ongoing experimental work (cf. (72) for an example of such experimental validation).

However, even the basic model can be employed to illustrate the emergence of a limited form of bistability, which may provide an important prerequisite for functional long-term plasticity as memory for brief signals to appear.

Receptor efficacy undergoes both negative (cAMP-dependent) and positive (calcium-dependent, RGS-mediated) feedback. There are two main regulatory loops, the PKA/PKC-mediated and GRK-mediated feedback. PKA/PKC are up-regulated by D1, and thus provides a *negative* feedback loop. GRK levels are influenced by internal calcium and thus constitute a *positive* feedback loop.

In general negative feedback leads to oscillatory dynamics with appropriate phase delays, while additional positive feedback can lead to the establishment of multistability (74).

The presence of antagonistic feedback effects suggests bistability mediated by calcium in the presence of slow oscillatory rhythms regulated by PKA. A simulation of the system shows the emergence of these features. The graph in Fig. 7 shows the induction and persistence of a state of high receptor efficacy by two calcium spikes.

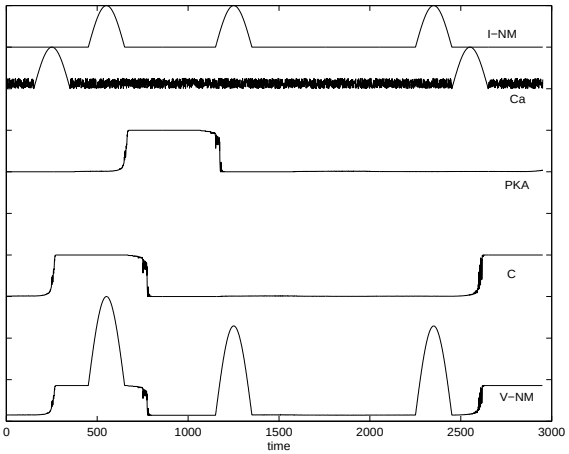

Fig. 7. Calcium-induced multistability of receptor efficacy. This simulation uses the model defined in Table 1, with a time delay for V_{PKA} $(\alpha_1 I_{PKA} + (\beta_1 V_{NM} - delay)))$. Brief triggering increases in calcium concentrations I_{Ca} induce changes in receptor efficacy C maintained by positive feedback and switched off by delayed increase in PKA-level. Actual receptor activation V-NM has different magnitudes for identical signals I_{NM}.

In the first case, the increase in calcium precedes a neuromodulatory signal.

Due to feedback effects, the increase in receptor efficacy C persists even when the calcium signal is terminated. Accordingly, the response of the receptor to this signal is increased compared to an agonist signal in the absence of calcium (second signal). This model also shows a critical dependence of response on the respective timing of Ca and I_{NM} signals, which should be testable empirically.

The existence of bistable or multistable states that persist beyond the duration of a trigger signal shows the realization of an important computational principle, the equivalent of a flip-flop device. This is a basic memory element and probably a necessary component for long-term plasticity of NM receptor efficacy. The critical dependence of efficacy on relative timing of calcium and NM signals opens up interesting perspectives for an interaction of NMDA and D1 related signals.

4 Long-term Plasticity of Neuromodulatory Receptors

4.1 Receptor super- and subsensitivity

Besides the short-term processes of densensitization and resensitization, there are also distinct processes of long-term regulation of NM receptor efficacy (75). Long-term alterations in receptor efficacy for membrane-bound responses can be measured directly by responsivity to agonist stimulation.

Both subsensitive and supersensitive populations of cells have been described in various tissues. Dopamine D1 supersensitivity has been shown in striatum after interruption of the dopaminergic nigro-striatal pathway (76) or in genetically altered dopamine-deficient mice (77). Exposure and withdrawal conditions for amphetamine or cocaine also change dopamine receptor sensitivity. For instance, there is D1 receptor supersensitivity in nucleus accumbens (78; 79; 80; 1; 81) and D2 receptor subsensitivity in nucleus accumbens (82; 79) and ventral tegmental area (79). Treatment with antipsychotic medication has also shown consistent shifts in receptor sensitivity in a number of brain areas (ventral tegmental area, prefrontal cortex, basal ganglia)(83; 84; 85). Furthermore, experiments after specific learning events such as socialization or restraint stress have been reported to affect receptor density. For instance, D2 receptor binding density in striatum is increased for socially dominant monkeys and reduced for subordinate monkeys (7) and induction of overexpression of D2 receptors in nucleus accumbens by genetic transfer in rats correlates with an increased resilience to alcohol addiction (86). Alterations in density of muscarinic receptors in neocortex and amygdala have been observed as the result of training in an inhibitory avoidance task (6; 87).

Receptor density can be indirectly assessed by the binding capacity of receptors to radioligands (for membrane receptors) or the amount of mRNA for a receptor (which comprises both internalized and membrane-bound receptor protein). With brain imaging (PET/SPECT), radioligand binding can even be measured in the living human brain (88; 89).

Similarly to short-term desensitization, receptor density tends to increase at low concentrations of agonist and decrease at high levels of stimulation. For instance, ongoing agonist stimulation ($>$ 4h) has been shown to result in long-term loss of membrane-bound receptor density for the dopamine D1 receptor in cultured cells (up to -50% of control with $t_{1/2}$= 8h, (90)). This basic homeostatic regulation is however embedded in a system of further regulatory factors, which allow storage and permanence of receptor localization and density. Thus, long-term shifts in receptor density and efficacy may also be the result of specific brief co-ordinated events that affect relevant parameters in a sustained fashion. In this sense, long-term plasticity in receptor density may have a memorization function that goes beyond adaptivity to current agonist concentrations.

Another question is the relationship between receptor density and functional receptor sensitivity. Often, receptor density is directly parallel to functional receptor sensitivity as measured by effects on membrane excitability or synaptic transmission. Thus agonist depletion produces both an increase in receptor density and an increase in electrophysiological responsiveness e.g. of beta-adrenergic receptors in hippocampus and cortex (91) or for opioid receptors after morphine withdrawal (92).

But increased sensitivity of a receptor may occur without an increase of receptor density. The pharmacodynamic response to agonist occurs in proportion to the quantity of the ternary complex agonist-receptor-G-protein, not just receptor protein abundance per se, or even membrane-bound receptor protein abundance (93; 94). Receptors can exist both in a state where they are coupled to GTP-free G-proteins (high affinity to agonists), or they may exist without the effector molecule G-protein coupled to it, the low affinity state (95). The supply of G-proteins is restricted in cells, such that there is competition for receptors to achieve a high affinity state. Experimental evidence has indicated that there are shifts in affinity of D2 receptors in nucleus accumbens after exposure to amphetamine, which can explain increases of D2-receptor mediated behavior, even though the total receptor density remains unaltered (96). In this case, D2 receptor supersensitivity is expressed by an increase in high affinity (G-protein coupled) receptor sites (97).

This form of plasticity has certain implications. If we assume that receptor localization on the cell membrane (i.e. at synaptic sites) is relevant for neural transmission, changes in affinity can modulate transmission without affecting

receptor localization. This may be important for the retention of the functional properties of the modulated system.

Finally, long-term alterations of receptor sensitivity may be expressed by alterations in intracellular pathways, such as a permanent upregulation of the cAMP-pathway (98). In this case the shift in sensitivity is not specific to the type of receptor but to the pathway being modulated, which is usually connected to a number of different receptors. Thus there is a third process available to effect long-term changes in receptor efficacy.

Detailed experiments on dopamine receptor sensitivity have been conducted in slices of rat brain after exposure to cocaine or amphetamine.

Sensitivity is here usually assessed by response threshold to different concentrations of agonist. For nucleus accumbens in cocaine-sensitized animals, a much lower dose of dopamine ($20\mu M$) elicits a electrophysiological response in D1 receptors than is required in control animals ($75\mu M$, (99)). The effect of the higher dose ($75\mu M$) is the same in the supersensitive and normal system (99). Thus there is a leftward shift in dose-dependence which is compatible with a change in the I_1 parameter for receptor efficacy (see eq. 4 above).

Alternatively, the normal response to NM modulation may become replaced by an ongoing "chronic" response and the cell becomes subsensitive or ceases to be responsive to agonist stimulation. This form of whole-cell plasticity is not dependent on neuromodulator receptors, but consists of a shift in the ion channel distribution and density that defines membrane excitability (e.g. (100; 101)). For instance, in cocaine-sensitized animals, some cells constitutively suppress the N- and P-type calcium channels that are normally suppressed by D1 receptor activation (102). The effect is a loss of NM responsivity on this parameter.

4.2 NM effects on neural transmission

The neural response is a product of both agonist concentration and the current receptor efficacy. Previous computational models that attempted to assess the function of neuromodulation on the basis of variable agonist concentrations (103; 104), assuming that receptor response would be uniform in space and time, may have failed to factor in the real receptor variability, which, as we have seen, is highly regulated and therefore likely to be of functional importance rather than only a source of unreliability and error ('noise').

Generally, neuromodulators have the potential to affect both synaptic transmission and intrinsic (whole-neuron) membrane properties. The synaptic effects of the D1 receptor, and NM receptors in general, concern the regulation

of transmitter release by presynaptic receptors and the regulation of NMDA-mediated glutamatergic transmission by postsynaptic receptors (105).

Neuromodulators also have diffuse effects on the membrane potential of the neuron, mediated by alterations in ion channel currents from receptors on the dendrite and soma in postsynaptic and non-synaptic positions (106; 107). The significance of whole-neuron modulation, however, is considerably less well investigated as a source of memorization and learning.

There is a consensus that both presynaptic D1 (108; 109; 110; 111; 112; 113; 114) and D2 receptors (115; 116; 117; 118; 119) depress the amplitude of evoked EPSP's in a number of different tissues with some debate as to whether the frequency of spontaneous EPSP's is similarly reduced (120; 114) or actually increased by presynaptic D1 receptors (121). A similar effect has been observed for the regulation of GABA release: both D1 and D2 receptors reduce evoked IPSP's (122; 123; 20; 124; 125; 126; 127). In postsynaptic position dopamine D1 receptors enhance NMDA transmission, by increasing peak conductance and lowering the threshold voltage for NMDA receptor activation (26; 128; 27; 129). There may also be an effect of dopamine D1 receptors on AMPA receptors via phosphorylation of GluR1 subunits at Ser^{845}, mediated by inhibition of PP1 and PKA (via DARPP-32, (130)) in striatal neurons. This conformational change increases the channel open time probability (in contrast to phosphorylation at Ser^{831} by PKC and caMKII, which increases AMPA channel conductance.) Thus dopamine may also be able to enhance peak AMPA current in specific dopamine D1 receptor rich areas of the brain.

On the neuronal level, the effect of neuromodulators on signal transmission is expressed by altering membrane excitability. However, it has been difficult to assess these effects precisely with the help of *in vitro* slices, and there is some disagreement concerning the effects of the dopamine D1 receptor. The D1 receptor enhances or reduces the contribution of a number of ion channels, such as high-voltage activated calcium channels (L-type calcium channels are enhanced in neostriatal spiny neurons (22), N- and P-type calcium channels are blocked (23)). It also affects sodium (25) and potassium channels (21).

The effects on neuronal firing patterns are obviously complex, since they depend on membrane voltage, the distribution and frequency of different ion channels and other events affecting ion channel currents.

4.3 Synapse- and cell-specific receptor regulation

We have seen that there is a significant body of evidence showing that NM receptors undergo experience-dependent long-term plasticity.

These results focus on the response of a *population* of neurons by examining a few selected neurons with the most pronounced alteration of response. Results are usually not reported with an emphasis on *cell-specific* variability. Nonetheless, there is often considerable heterogeneity with respect to reactivity to NM's within a population of neurons in a slice (J. Seamans, pers. comm., for dopamine D1 and D2 receptors in deep-layer prefrontal cortical cells) with 'high responders' and 'low responders' within a neuronal population. Visual inspection also shows a varying number of fluorescent-labeled receptors on cultured cells, e.g. transfected with D2 receptors (131), which is understood as an individual variability of receptor distribution and density (S. Rayport, pers. comm.). Cellular binding patterns for dopamine receptors are different for different neurons also in striatal slices (132),(133),(134). New techniques of laser capture microscopy may be able to give clear answers on the question of cell-specificity (M. Ariano, pers.comm).

There are also results indicating that receptor density may vary in 'patches' of (subcortical) tissue or microcolumns in cortical tissue (135). For instance, fear conditioning influences muscarinic receptor density differentially in different regions of the amygdala (87), (136).

Synapse-specific regulation has been shown conclusively in the short-term (137). NM receptors in synaptic positions are also anchored by scaffolding and anchoring proteins, which indicates that positioning of membrane receptors at a specific site is relevant to NM receptor action (138; 139). Thus, the basic mechanisms for synaptic long-term plasticity exist. Very recently, (140) have actually shown direct synaptic plasticity at cholinergic synapses in hippocampus.

4.4 Functional consequences of long-term plasticity

We have argued that the effects of neuromodulation on neural transmission are not sufficiently described by the fluctuations in the concentration of agonist, but require an analysis of receptor sensitivity as well. This means that the responsivity of the cell as expressed by receptor density and efficacy will determine the net effect on neural transmission.

The consequences of this regulation are somewhat different, whether we look at this from the perspective of a homogeneous shift in sensitivity in a particular brain area, or whether we assume cell-specific effects to be present under physiological conditions.

Thus the plasticity located in the receptor and its internal transduction pathway could be *functionally* significant at the level of the individual cell and the synapse. This could be the case for both short-term and long-term plasticity.

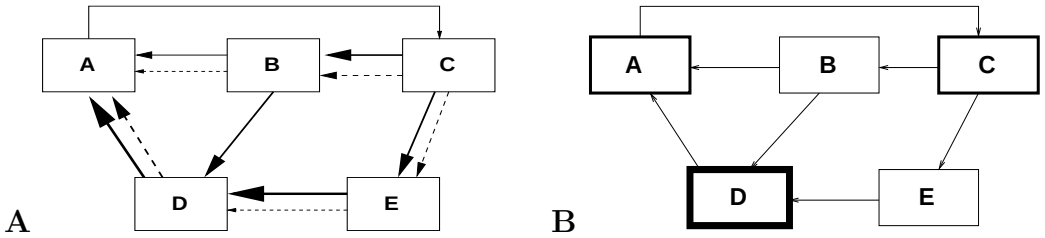

Fig. 8. Two expanded views on information storage in neural networks. A: Processing units are linked by connections of differing strengths. Overloading and switching allows fast modification of synaptic strengths. B: Processing units differ by their activation of transfer function. Neurons with different membrane properties interact in a 'heterogeneous' network.

Long-term plasticity in the responsivity of neurons and synapses to a neuromodulatory signal implies a mechanism of *information storage* that is expressed by the placement of NM receptors leading to an individual cell signature. Thus, NM receptor plasticity adds a layer of storage capacity to neurons and synapses which allows memorization other than through Hebbian processes (see Fig. 8). This hypothesis is considerably different from the widespread assumption that neuromodulation influences a global parameter for neural transmission which is uniform for all cells and synapses in a targeted brain region (104; 141).

Synapse-specific regulation of NM receptor efficacy and distribution specifically adds an important dimension to traditional accounts of long-term potentiation (LTP) and long-term depression (LTD), which focus on the contribution of the glutamatergic pathway. It introduces additional variables which determine the magnitude of change of glutamate synaptic transmission when presynaptic NM receptors are activated and postsynaptic receptors interact with NMDA, AMPA or $GABA_A$ receptors. A NM signal-gated change in synaptic "weight" reflects a synapse-specific fixed parameter (namely the presence, absence or magnitude of a NM receptor mediated effect). The presence of a strong, phasic increase of NM concentration will then result in "fast synaptic switching" (Fig. 8 A). This means that synaptic connections can be quickly and reversibly set to a new weight, without interfering with any long-term properties of the glutamate transmission. Technically, this corresponds to "overloading" of synaptic connections with several possible synaptic weights each of which can be switched on by activation of appropriate NM receptors. Such mechanisms have occasionally been suggested in order to add to the known capabilities of neural networks (142; 143). In (144) it was shown that template switching by neuromodulator control of presynaptic release is particularly amenable to the idea of state-dependent task performance, which is a major biological function of neuromodulation.

4.5 Implications for brain plasticity

The idea that neuromodulation contributes to long-term potentiation and long-term depression, influencing the magnitude of change in glutamatergic transmission, has been around for a long time. A number of experimental results have been obtained that support a measurable difference for LTP/LTD in the presence or absence of high levels of neuromodulators, such as dopamine (145; 146). In this context, the theoretical concept of 'metaplasticity' has been developed (147), cf. (148). This concept assumes a level of regulation for glutamatergic plasticity that is not dependent on Hebbian associativity of pre- and postsynaptic firing ('meta'-level). Another idea that forms the basis of a number of computational accounts of dopamine-related plasticity (149; 104) is 'three-factor Hebbian plasticity', i.e. regulation of glutamatergic signalling strength that requires a 'third factor', namely dopamine, in addition to concurrence of presynaptic and postsynaptic events. Both approaches, however, do not challenge the idea of glutamatergic signalling as a 'final common pathway' for different sources of plasticity and the changes in glutamatergic signalling as the substrate for learning.

In contrast to that, we have aimed to show that there is a significant motivation from the perspective of molecular biology that receptor plasticity is an ubiquitous phenomenon which may have become recruited for learning and memorization for a number of different neurochemicals. We have also reported here that there is convincing electrophysiological evidence that shifts in receptor sensitivity do occur in the long-term, even though specificity for individual cells and synapses is not well proven. The exact relationship of this form of plasticity to physiological brain adaptivity is at present virtually unknown.

The effects of NM receptor activation on *intrinsic properties* of the neuron - expressed by membrane excitability and ion channel activation - add a significant dimension to brain plasticity. The most prevalent view of neural plasticity as altering the strength of connections between neurons is changed considerably, when we accept whole-neuron adaptive plasticity (Fig. 8 B).

This role of whole-neuron plasticity within network processing has occasionally been explored from a theoretical perspective (cf. (107; 150)). The alteration of membrane properties due to neuromodulation or a specific composition of ion channels induces a 'filter' on signal transmission that may affect gain modulation (151) or short-term retention of spike input patterns (152). A significant difference in receptor density and sensitivity will affect the efficacy of the intrinsic 'filter' for each individual neuron.

NM receptor regulation is specifically interesting for its property of 'conditional' plasticity. This means that differences in parameter setting are greatly

enhanced when a sufficient amount of agonist is present to engage NM receptors. The functional implications of NM receptor plasticity will be virtually non-existent or very strong depending on fluctuations in agonist concentration or the presence of an agonist signal.

5 Conclusion

Even though the relevance of the biological processes underlying G-protein coupled receptor regulation to addiction research and psychopharmacology is frequently asserted (98), we still do not have a good understanding of the physiological function of this form of plasticity.

The simplest theory would assert that receptor regulation is essentially a homeostatic control mechanism to counteract the significant fluctuations in agonist availability. In this scenario, the goal of receptor regulation is to ensure a target range of NM effectiveness.

Certainly that is a very important function of receptor regulation from a metabolic perspective. But the presence of multiple, nested feedback loops in a complex, highly regulated system suggests the presence of multistable solutions. The presence of receptor anchoring adds the necessary stability to transform transient fluctuations at synaptic sites into permanent values.

In this paper we have focussed on the hypothesis :

(a) that neural information processing is influenced by the *combination* of the neurochemical signal (the agonist concentration) and the receptor response (the receptor efficacy or sensitivity),
(b) that receptor efficacy is regulated on the level of the synapse and the neuron, and
(c) that long-term plasticity of NM receptors is functionally significant in *information storage*.

The regulation of agonist concentration is of course another important factor in understanding neuromodulation. Even though short-term changes are mainly a result of firing of the producer cells, transporter availability is another major factor that undergoes a form of functional plasticity (153; 154; 155).

Other questions that require experimental analysis are the conditions that trigger the transition from short-term to long-term plasticity and the behavioral paradigms that influence long-term receptor density and placement. Certainly, further experimental evidence is required to explore the validity of this hypothesis.

Another important conclusion of this work is that the role that NMDA activation, calcium influx and enhanced protein synthesis play in a large number of behavioral learning experiments may have to be re-assessed without automatic reference to the 'dogma' of glutamatergic synaptic plasticity as the neural substrate of learning and memory. In contrast, NMDA- and calcium- related induction could point to a common, integrated perspective on neural plasticity, encompassing glutamatergic/GABAergic transmission, neuromodulation and the regulation of internal cell processes.

We conclude that we need to pursue integrated models of neural and synaptic plasticity, which combine AMPA and glutamate related plasticity and NM related plasticity into a single model. Fundamentally new theoretical abstractions need to be developed that can provide a guideline in the experimental testing of their implications. Essentially we will have to explore the agonist-dependence of NM receptor sensitivity and the concept of conditional plasticity as the basis of "learning rules" for neuromodulation (e.g., (156)).

Non-traditional sources of plasticity that may contribute to models of memory and learning are not restricted to plasticity in NM receptor activity. They include long-term alterations of the distribution of ion channels, morphological alterations in spine density and dendritic branching, and levels of gene expression for a number of proteins affecting intracellular pathways.

The fundamental dogma of Hebbian plasticity - associative strengthening of the synaptic connections that mediate fast neural transmission as neural substrate for learning - may have to be reconsidered.

The modification of synaptic connections has undoubtedly a major role in experience-dependent plasticity - but the idea of associative strengthening based on the co-occurence (or, in more modern views, the precise timing) of pre- and postsynaptic activity may have to be embedded in a more comprehensive view, involving NM induced switching, overloading of synaptic values, or adaptive regulation of coupling strength. In general, the processes that govern cross-signaling in transmitter release are not sufficiently understood, but undoubtedly of importance in understanding synaptic plasticity, as well as the interaction of NM receptors with glutamate and GABA receptors in the postsynaptic domain.

But besides that, we may have to further investigate the role of whole-neuron plasticity in learning and memorization. This involves the storage of experience by cellular parameters and performing read-out by alteration of membrane properties that affect the transfer function.

In the light of the major potential sources of cellular plasticity uncovered by molecular biology, it may well be that the most significant models on the neural substrate of behavioral learning and memorization are yet ahead of us.

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